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Understanding the Brain

Course Guidebook

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PUBLISHED BY:

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Professor Jeanette Norden is a neuroscientist and Professor of Cell and Developmental Biology in the School of Medicine and Professor of Neurosciences in the College of Arts and Sciences at Vanderbilt University. She received her Ph.D. in Psychology, with training in Neurobiology and Clinical Neurology, from Vanderbilt University. She completed postdoctoral training at Duke University, the National Institute for Medical Research in London, and Vanderbilt School of Medicine.

For more than 20 years, she conducted research on nerve regeneration, focusing on GAP-43, a protein involved in nervous system development, regeneration, and plasticity. Since 1997, she has devoted her time to medical, graduate, and undergraduate education. She is currently the Director of Medical Education in the Department of Cell and Developmental Biology. She has been a maverick in medical education, stressing not only intellectual but also personal and interpersonal development in students. Her emphasis on personal development and her innovative approach in integrating "humanity" into basic science courses has been recognized at Vanderbilt and nationally.

She has won every award given by medical students, including the Shovel twice (given by the graduating class to the faculty member who has had the most positive influence on them in their four years of medicine), the Jack Davies Award six times (for teaching excellence in the basic sciences), and the Outstanding Teacher of the Year Award four times. She was also awarded the first Chair of Teaching Excellence at Vanderbilt University, and she was the first recipient of both the Gender Equity Award of the American Medical Women's Association and the Teaching Excellence Award given by the Vanderbilt Medical School. In 2000, Dr. Norden was the recipient of the Robert J. Glaser Award, a national teaching award from the Alpha Omega Alpha Honor Society of the American Medical Association.

Dr. Norden participates in numerous outreach programs in Nashville, Tennessee, and the surrounding communities by going to schools and by giving public talks on psychoactive drugs, the aging brain, and other topics related to the neurosciences. For a number of years, she has taught extremely popular courses in neuroscience for the Osher Lifelong Learning Institute at Vanderbilt.

Dr. Norden has traveled internationally to give scientific presentations, talks, and workshops on teaching, and to teach medical school (Nepal); in 2004, as part of a cross-cultural humanitarian and educational program in palliative care, she was a delegate to HIV/AIDS clinics in rural South Africa.

Dr. Norden has served as a member of the Neuroscience/Neurology Task Force for the National Board of Medical Examiners, and she has served as the external reviewer for a Keck Foundation grant to revise undergraduate science education in 16 colleges in the South. Dr. Norden was highlighted as one of the most effective teachers in America in *What the Best College Teachers Do* (K. Bain, Harvard University Press, 2004). ■

Acknowledgments

It is a pleasure to acknowledge the support and generosity of my friends and colleagues. A number of individuals, including Drs. James Fix, Troy Hackett, and William Whetsell, provided images used in *Understanding the Brain*. Christopher Ciarleglio is especially thanked for his wonderful drawings. I also want to thank Pamela Greer, Alisha Reay, Megan Herron, and all of the camera and production team at The Teaching Company. I cannot imagine a better team with whom to work. A special thanks to my delightful "audience," Peter, Lise, Wayne, Sandy, and of course, Keeper. Last, but not least, I want to thank my friends Susan and Philip Samson, who read early drafts of the outlines, made valuable suggestions, and encouraged my participation in this project; Marc Wozniak, who helped with any and all computer "issues"; and Robert Williams, who demonstrated extraordinary patience, support, and affection through it all.

In memory of
John and Helen Norden,
Who first taught me the value of an education
and
Reah Wehir
and
Robert C. Solomon,
Teachers *extraordinaire.*

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Disclaimer

These lectures are intended to increase the understanding of the structure and function of the human brain. They are in no way designed to be used as medical references for the diagnosis or treatment of medical illnesses or trauma.

Neither The Teaching Company nor Dr. Norden can be held responsible for any result derived from the use of this material. Questions of diagnosis or treatment of medical conditions should be brought to the attention of qualified medical personnel. ■

Understanding the Brain

Scope:

> **"The mind is just the brain doing its job."**
>
> Simon LeVay
> *The Sexual Brain* (1993)

As humans, we are fascinated by *ourselves,* by the qualities and abilities that seem to separate us from the rest of the animal world. But how different are we really? What is the basis of these differences? While some might argue that we alone have "souls," science cannot offer any evidence one way or the other. Science, as an approach to answering questions about the natural world, however, may be able to shed light on how our brains have been shaped by evolution in such a way that particular abilities are unique, or at least developed to an extraordinary degree, in our species. Thus, while other animals may experience the world, act with intent, and even use tools, we think, reflect, and communicate symbolically. We also have a sense of ourselves as sentient and mortal beings, making humans alone likely to have spiritual yearnings—and to be in need of—a soul.

Understanding the Brain is designed as a survey course to introduce individuals without a background in science to the modern field of neuroscience. Drawing on everyday experience and popular books, as well as current research, the course seeks to amaze and inform the learner about this remarkable structure. The course is divided roughly into four segments. It begins with introductory lectures on how the central nervous system is organized at gross, cellular, and molecular levels, including a brief look at how this incredibly complex organ arises during development (Lectures 1–11).

In the second segment of the course, we explore how the brain and mind might be related by looking at how different areas of the brain appear to be actively involved in the creation of mental percepts arising as the result

of our interaction with the external world through our senses. This section ends by looking at how movement is initiated and coordinated, and how the interpretation of incoming sensory information by the brain helps guide and modify action (Lectures 12–19).

In the third section of the course, we discuss brain areas that are believed to underlie language, emotion, executive function, and cognition (Lectures 20–29). Lectures in the fourth and last segment of the course (Lectures 30–36) deal with selected topics chosen because they are of universal interest. These include lectures on sexual dimorphism of the brain, sleep/dreaming, consciousness, and the development of a *self*. The last lectures in this section focus on how our perception and emotions affect us as individuals, in terms of both our emotional and physical health. We will end this segment and the course with a general discussion of the types of questions neuroscience is currently addressing, as well as by raising the issue of the potential limitations of understanding the mind through the study of the brain.

Throughout the course, there are frequent reviews of previously covered material and use of examples from clinical neurology that give insight into the functioning of both the brain and the mind. Clinical examples are explained in a straightforward way and will be of common neurological disorders such as stroke, Parkinson's and Alzheimer's disease, and also of more rare brain disorders and conditions.

A common theme throughout the course is that the brain represents the biological substrate of the mind. One of the most distinguishing features of what our minds do is to make meaning of the world; this is true whether we are *seeing* a vase, or *pondering* our own mortality. Through the workings of our minds whose biological substrate is the brain, we make *meaning* of our lives and experience. This meaning can then be used to guide behavior, providing an enormous advantage to our species in terms of adaptability. ■

Historical Underpinnings of Neuroscience

Lecture 1

This course as I've designed it is a broad survey course for individuals without a background in neuroscience and, in fact, you don't have to have any background in science at all to understand it. All you need to do is bring to this class your interest in learning something about the human brain.

The modern field of neuroscience rests on a foundation of knowledge built by both scientists and nonscientists in a pursuit of understanding how we know about our world and what constitutes the biological substrate (or even if there is one) of our experience. Here we explore some of the more significant historical and intellectual underpinnings that have led from the view that the brain is essentially irrelevant—to the modern conception of the brain as the biological substrate of the mind.

This course is designed as a broad survey course for individuals without a background in science. The course itself is divided into roughly four segments. The first 11 lectures will introduce you to how the *central nervous system* (CNS) is organized at gross, cellular, and molecular levels—and how this incredibly complex structure emerges during development. Lectures 12–19 explore how the brain and mind are thought to be related, beginning with three of the sensory systems (visual, auditory, and somatosensory), and ending with a discussion of the motor system. Lectures 20–29 cover higher-order *cognitive* functions (language, learning, memory, emotion, and executive function).

For the last segment, through Lecture 36, we will address a number of general interest topics, ranging from whether the brains of males and females are different to how the brain is thought to regulate sleep and dreaming and even *consciousness*, and the very development of a "self." We will also discuss *Alzheimer's disease*. We will end the course by summarizing what we have learned about the brain, and what questions are currently of great interest to neuroscientists.

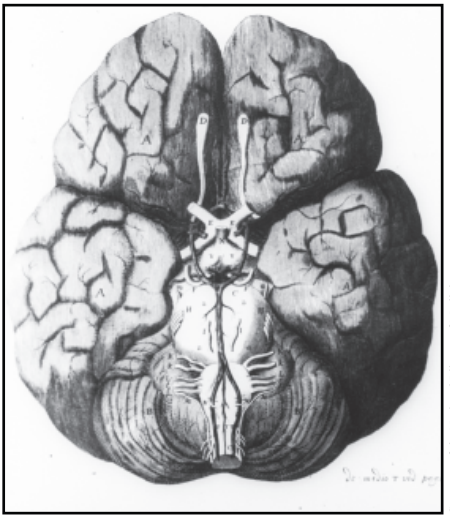
We begin our course with an historical introduction. One of the reasons we begin here is because neuroscience is, and has always been, an eclectic field, formulating and refining theories based on experimental research, but also borrowing ideas, historically, from other disciplines such as philosophy. In this first lecture, we can touch only briefly and superficially on the historical antecedents of modern neuroscience, and on some of the most important of the paradigm shifts which have occurred from antiquity to the present in our thinking about mind, soul, and brain.

Ancient civilizations believed the heart was the seat of cognition and of the "soul." Records from ancient Egypt indicate that sometime around 1000 B.C., the brains of Pharaohs, and others deemed worthy of embalming, were extracted through the nose and discarded; the heart, on the other hand, was believed to be of ultimate importance, and it was left in place to be mummified with the body; the Pharaoh could enter the afterlife without a brain, but not without a heart.

Other ancient peoples around the Mediterranean, including the Greeks, as well as those of India and China, likewise held the heart to be the organ and seat of intellect, memory, emotions, and the spirit or soul of the individual. Aristotle (384–322 B.C.), who influenced both science and philosophy for centuries, held firmly to the belief that the heart was the seat of cognition and perception. In his philosophical system, the brain functioned only to cool the passions of the soul or heart. Later, Galen (c. 130–200 A.D.), a Greek physician in Rome whose theories dominated until the Renaissance, would reject Aristotle's belief that the heart was the seat of the soul or mind, but he did not let go of the idea that the soul or mind consisted of "spirits" that emanated from the heart; the role of the brain was to make these spirits "noble."

Beginning during the Renaissance, the soul and mind became localized, if not always to the brain, at least in the head. One of the earliest theories was that *perception*, memory and other cognitive functions resided in the *ventricles*, which are essentially holes in the brain; the Renaissance genius Leonardo da Vinci (1452–1519), who provided us with some of the most detailed and accurate depictions of the ventricular system of the brain,

believed that perception and cognition resided in these cavities, and not in the brain substance itself.



Courtesy of the National Library of Medicine.

In the modern era, the brain is seen as the biological substrate of the mind.

Of the many philosophical influences on modern neuroscience, surely one of the most influential was that of the French philosopher and mathematician René Descartes (1596–1650) whose name has become almost synonymous with *Dualism*, the belief that mind and body are distinct entities that are independent and different in nature. Descartes spoke of the bodies of animals and humans as machines driven by biological processes; he believed, however, that the mind or *rational* soul was found only in humans. Descartes sought to identify the place where this soul might interact with the body; he believed that the pineal, a single unpaired structure in the brain, might be the "seat" of the rational soul. This seems an interesting conclusion in view of the fact that animals have a pineal gland.

Later, individual scientists/physicians/philosophers began to believe that the brain was responsible for many of the functions previously attributed to a "soul." In the 17th century, the English anatomist and physician Thomas Willis (1621–1675) became the father of neurology, the field of medicine involved with disorders of the brain. Willis's observations, in conjunction with the beautiful and detailed anatomical drawings of Christopher Wren (1632–1723), later England's great architect, helped establish that perception, movement, cognition, and memory were all functions of the brain substance itself.

Lastly, even a superficial history would not be complete without mention of Franz Joseph Gall (1758–1828) who believed the brain was the organ of the "mind." Gall postulated that complex mental functions (for example, generosity) were associated with areas of the outer part of the brain or *cerebral cortex*, and that the development of various faculties was reflected in the shape and size of areas of the skull. These ideas became formalized in the field of *phrenology*; it was not until after Gall's death that his ideas began to be challenged by the individuals who would provide the foundation for modern experimental neuroscience.

Neuroscience does not address and cannot address questions related to whether there is a soul, whether there is some kind of quality present in humans that survives the death of the brain and the death of the body.

This very brief introduction cannot possibly do justice to all of the individuals, especially within psychology and philosophy who, from antiquity to the present time, have asked the questions which are only now being addressed by neuroscientists: "What do we know of the world in which we exist?" "How do we know it?" "What is the mind?" These and other *epistemological* and *ontological* questions are still central to both philosophy and to neuroscience, although they are framed differently in the two disciplines. In the modern era, the brain is seen as the biological substrate of the mind; neuroscience cannot address questions related to whether there is a soul, separate entity, ethereal quality, or spirit that survives the death of the brain; the emphasis in modern neuroscience is to understand the brain, and ultimately how the brain and mind are related. ■

Suggested Reading

S. Finger, *Origins of Neuroscience.*

C. Zimmer, *Soul Made Flesh.*

Questions to Consider

1. How many sayings or expressions can you come up with that show how our use of language still reflects an earlier view that our feelings relate to our hearts and not to our brains?

2. Do you think there is a soul separate from the brain? How would this soul be related to a biological structure such as the brain?

Central Nervous System—Gross Organization

Lecture 2

The truth is that every single thing you can hear, feel, see, every thought you think, is the result of brain processes.

Before we can discuss the modern view of brain as the biological substrate of the mind, we need to define some terms that will be used throughout the course, and to understand something about the gross or overall organization of the brain. The *central nervous system* (CNS) refers specifically to the brain and spinal cord; the brain is continuous with the spinal cord through an opening in the skull (foramen magnum). The *peripheral nervous system* (PNS) consists of neurons and/or nerves located outside of the brain and spinal cord. An example is the sciatic nerve that runs down the back of the leg.

If we looked at the CNS from the outside, we would see the following parts: (1) The *spinal cord*, which is protected by our bony vertebrae. (2) Part of the *brainstem*, which is a phylogenetically older area of the brain continuous with the spinal cord. And (3) the *hemispheres*; in humans, much of the brainstem is covered by the two cerebral hemispheres.

There are a number of reference terms that are used to refer to different areas of the brain and spinal cord, and to the relative position of structures; some of these terms are shown in relation to a drawing of the brain in Figure 2.1.

- The terms *rostral* (towards the front or "head" end; anterior) and *caudal* (towards the back or "tail" end; posterior) are used generally to refer to the front and back of the brain, respectively.

- The terms *dorsal* and *ventral* are used to refer to the top and bottom (or underside) of the brain.

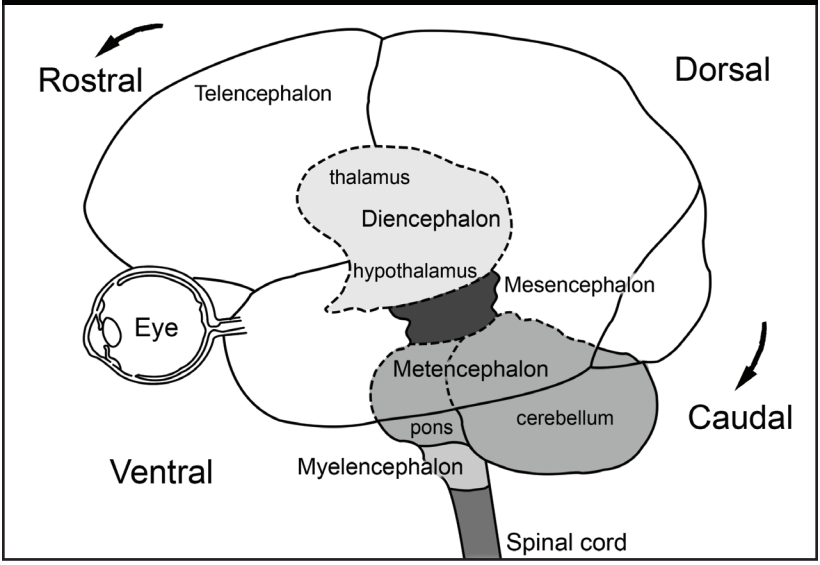
- The terms *medial* and *lateral* are used in reference to the body midline with medial towards, and lateral away from, the midline.

The adult brain can be subdivided grossly along a rostral-caudal dimension into five regions (Figure 2.1); how these regions develop will be one of the topics of a future lecture.

- The *telencephalon* is the rostral-most subdivision of the brain consisting of the two cerebral hemispheres; the telencephalon is the most recently evolved area of the brain and its function will be the focus of many lectures in this course exploring the relationship between mind and brain. It is the outer surface of the telencephalon (cortex), which is believed to be the seat of the mind.

- The *diencephalon* includes the thalamus (anteroom), an important structure consisting of a number of distinct areas/structures, many of which will project to (e.g., be connected to) the cerebral cortex, and

Figure 2.1



A drawing of the brain and spinal cord to illustrate how rostral/caudal and dorsal/ventral are defined in relation to the brain. In this drawing, the face of the individual would be rostral, and the back of the head caudal. The five major subdivisions of the adult human brain are also shown.

hence the name "anteroom"; the *hypothalamus* which is "below" the *thalamus* and also composed of a number of individual areas, is responsible for the central control of *homeostasis* in the body.

- The *mesencephalon* or *midbrain*, lying between the diencephalon and the metencephalon; a number of structures in this part of the brain are involved in reflexes.

- The *metencephalon* ("between" brain) consists of two major structures, the *cerebellum* (the large ball-shaped structure at the base of the brain), and the *pons* (bridge) which connects the cerebellum to the rest of the brain.

- The *myelencephalon* (long white marrow structure) is also referred to as the *medulla* or *medulla oblongata*, and is so-named because it contains many of the long *pathways* or *tracts* (axons or processes of neurons traveling together in a bundle) in the brain, for example, axons projecting to the spinal cord; it is the medulla which is continuous with the spinal cord at the *foramen magnum*.

Other general terms are also commonly used to refer to different brain subdivisions.

- The *forebrain* refers to the rostral-most subdivisions of the brain, and includes the telencephalon and the diencephalon; the forebrain is the most recently evolved area of the brain phylogenetically.

- The *hindbrain* consists of the caudal brain subdivisions and includes the metencephalon and the myelencephalon. For example, the medulla would be considered a structure of the hindbrain; the hindbrain is considered a phylogenetically older or more primitive part of the brain, controlling vital, but largely unconscious or subconscious, functions such as breathing and heart rate.

- The *brainstem* is a collective term used to refer to the mesencephalon, metencephalon, and myelencephalon; like the hindbrain, the brainstem is considered an older area phylogenetically.

In the next lecture, we will see that internally, the brain is also organized into different areas. ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. What are the five subdivisions of the adult human brain from rostral to caudal? Why do you think the telencephalon is so large in humans?

2. Sometimes the meaning of a name gives a clue to its function. Why is the thalamus the anteroom?

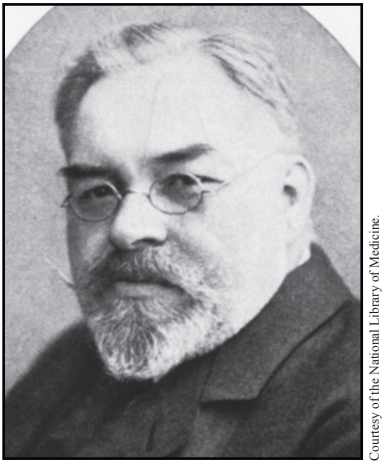
Central Nervous System—Internal Organization

Lecture 3

What we want to do now is to look at the complexity of the internal organization of the brain's subdivisions.

When early neuroanatomists cut open and viewed the internal part of the CNS, they noted that in fresh tissue some areas appeared "grayish" and other areas appeared "whitish" by contrast. We still use these terms in modern neuroscience, saying that the CNS is made up of two types of matter: *gray matter* and *white matter*. To understand how these terms are commonly used, and to what they refer, we need to be familiar with the parts of a *neuron*. The major parts of a neuron are the cell body, *dendrites*, and the *axon*. A generic neuron is drawn in Figure 3.1.

In the 19th century, when stains were developed and applied to sectioned brain tissue, it was discovered that gray matter consisted of aggregations of neuron cell bodies; groups of neurons that form functional and structural areas in the nervous system are called nuclei (singular = nucleus). A *nucleus* is a collection of neuron cell bodies into a structure with unique *cytoarchitecture*, connections, and function. Franz Nissl (1860–1919) developed a method for cutting the brain into thin sections and staining the sections with a dye that stained structures (*organelles* called "Nissl bodies") within neuron cell bodies. Nissl stains can be used to stain neuron cell bodies, but not their *processes* (axons and dendrites), and thus can be used to identify nuclei in the brain.

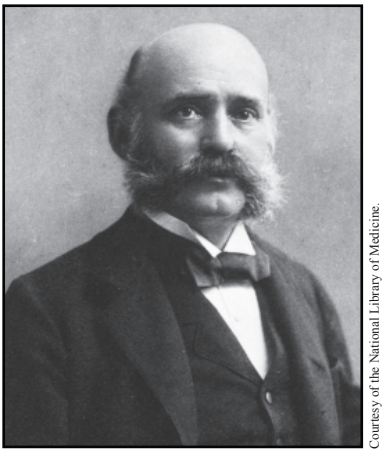


Courtesy of the National Library of Medicine.

Franz Nissl.

Using other techniques, it was discovered that the white matter of

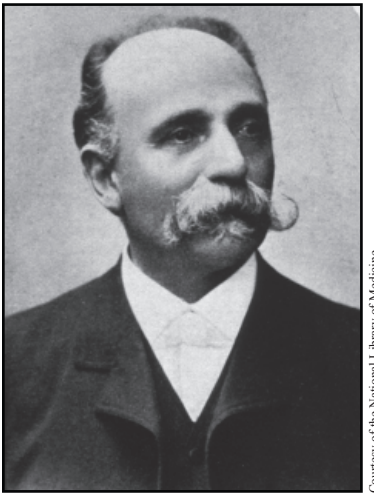
the CNS was composed of neuronal axons; what actually looks "white" in the fresh brain is the fatty *myelin sheath* that surrounds most axons (Figure 3.1). Karl Weigert (1845–1904) first developed a method for staining the myelin sheath. We can view white matter areas of the brain by using stains which selectively stain myelin (e.g., a Weigert stain), or stain structures inside of axons, or by injecting substances into the brain and filling the axons with a substance that can be visualized.



Courtesy of the National Library of Medicine.

Karl Weigert.

Finally, in a special method developed by Camillo Golgi (1843–1926), silver is used to fill or "impregnate" neuron cell bodies and dendrites (but not axons in the adult CNS); the Golgi method can be used to distinguish between neuron types on the basis of their dendritic trees or arbors. We have found that there are about 150 kinds of neurons based primarily on differences in their dendritic arbors, making neurons the most diverse cell type in the body. In modern neuroscience, we can inject various dyes directly into individual neurons and visualize their dendritic trees and processes.



Courtesy of the National Library of Medicine.

Camillo Golgi.

By using various methods or a combination of methods, the internal organization of the CNS, which is not visible from the external surface, can be revealed. When looking internally, we can view the ventricles and

Figure 3.1

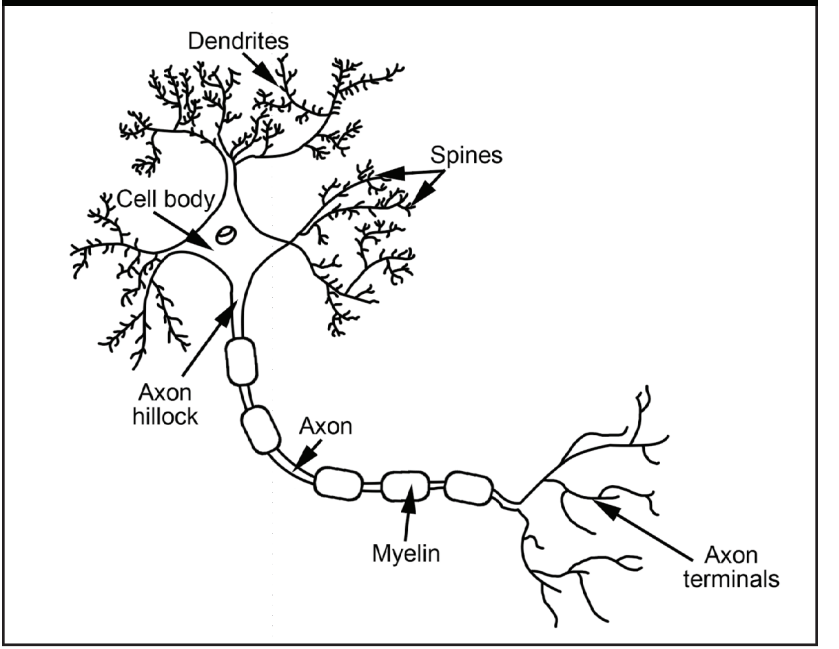


Figure 3.1: A drawing of a "generic" neuron. Dendrites are extensions of the cell body, and the axon is a specialized portion of the neuron (arising at the axon hillock) that connects neurons in different areas. Surrounding the axon is a myelin sheath, separated by small sections of exposed axon.

individual nuclei throughout the brain and spinal cord. Thus, we see that the brain and spinal cord are made up of a number of individual nuclei (gray matter) with bundles of axons coursing between them (white matter). ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. Would an area stained with a Nissl stain be considered white matter or gray matter? Why?

2. Approximately 150 different neuronal types can be distinguished on the basis of their dendritic trees. What specific method could be used to visualize dendritic arbors?

Central Nervous System—Subdivisions

Lecture 4

There are huge numbers of individual structures in the brain, ... and this is part of why it's been so complex and difficult to understand.

Each nucleus of the brain is a collection of neuron cell bodies constituting a structure with its own unique cellular organization (cytoarchitecture), connections to other neurons, and function. An understanding that the brain is divided into functionally distinct, although interrelated, areas is important for an appreciation of the rest of the material in the course.

Research has revealed that the nuclei of the CNS can be grouped together into functional systems, some with a single unifying function. For example, a large number of nuclei or areas play a role in motor behavior; collectively, these nuclei make up the "motor system" of the brain; each nucleus/area will have a specific function related to motor behavior. Other nuclei are sensory in function; for example a large number of nuclei of the brain process visual information and are thus part of a "visual system."

Another way of dividing the CNS into functional groups relates not to a specific function like vision but to a general group of functions. For example, the hypothalamus, a structure of the diencephalon, maintains homeostasis in the body; individual nuclei in the hypothalamus have roles in behaviors as different as body temperature, eating, or drinking. Another example would be the *limbic system*, a large number of nuclei involved in learning, memory, emotion, and executive function. The *reticular formation*, which consists of more than 100 individual nuclei, is another functional subdivision of the CNS; individual nuclei within the reticular formation play a role in regulating a variety of vital functions (like heart rate and breathing), and also sleep/dreaming, and consciousness. All of these different systems and their nuclei make up the gray matter of the brain.

Pathways/tracts, which represent groups of axons, make up the white matter of the CNS; these can also be subdivided into a number of different functional types.

- *Association pathways* are axons that connect different areas of the *cortex* within each hemisphere. An example is the *cingulum* (girdle), an association fiber bundle consisting of axons of *cingulate gyrus* neurons that connect various *lobes* within each hemisphere.

- *Commissural pathways* are axons of neurons that connect an area in one hemisphere with the same area in the other hemisphere. The major commissural pathway in humans is the *corpus callosum*, connecting *homotopic* (same) parts of the cortex in both hemispheres.

- *Projection pathways* are made up of axons "projecting" out of one area to connect with another area of the brain.

    - As shown in Figure 4.1, neurons located in the cortex, which are involved in the initiation of a motor movement (motor cortex), project their axons (via the corticospinal tract) to the spinal cord; neurons of the spinal cord then project their axons to the muscle to produce contraction and movement.

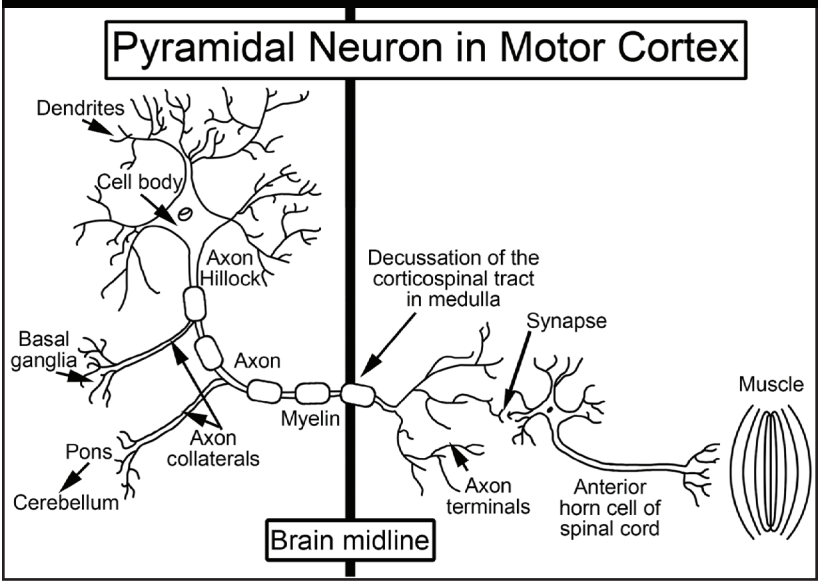
    - The motor cortex on one side of the brain controls the movement on the other side of the body because the projection axons cross the *midline* (or *decussate*) to enter the spinal cord on the opposite side.

[The] circuit board only has about 20 components on it. There are 100 billion neurons in the adult human brain. And there are estimated to be 100 trillion connections between them.

Often, as in the corticospinal tract, the pathway or tract is designated in a way so that the first term (cortico) is where the cell bodies of origin lie, and the second term (spinal) refers to where the axons of these neurons synapse or make a connection with other neurons. While there are other ways the brain and spinal cord can be subdivided, these are the major ways that will be useful in understanding the ensuing lectures in this course.

All of the components in our brain are connected to each other, the axons, and they all have a specific function. These would be the nuclei and what they do. But we don't have a blueprint. This is why all these early techniques and everything were developed, so that we could even identify where the nuclear groups were at, or identify where the axons went, and now to understand what the function is. Think of it this way, a circuit board only has about 20

Figure 4.1



A drawing illustrating a pathway in the brain. Shown is one neuron in the motor cortex projecting its main axon (in the corticospinal tract) to the spinal cord. Note that the axon decussates (crosses) to the opposite side of the brain before entering and synapsing in the spinal cord.

components on it. The adult human brain has 100 billion neurons and about 100 trillion connections between them. ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. Is the organization of the brain how you conceptualized it? If not, how is the organization different from what you expected?

2. How does understanding how the brain is organized into areas help you appreciate why specific functions might be lost, for example, in an individual with a brain tumor?

Cortex—Lobes and Areas

Lecture 5

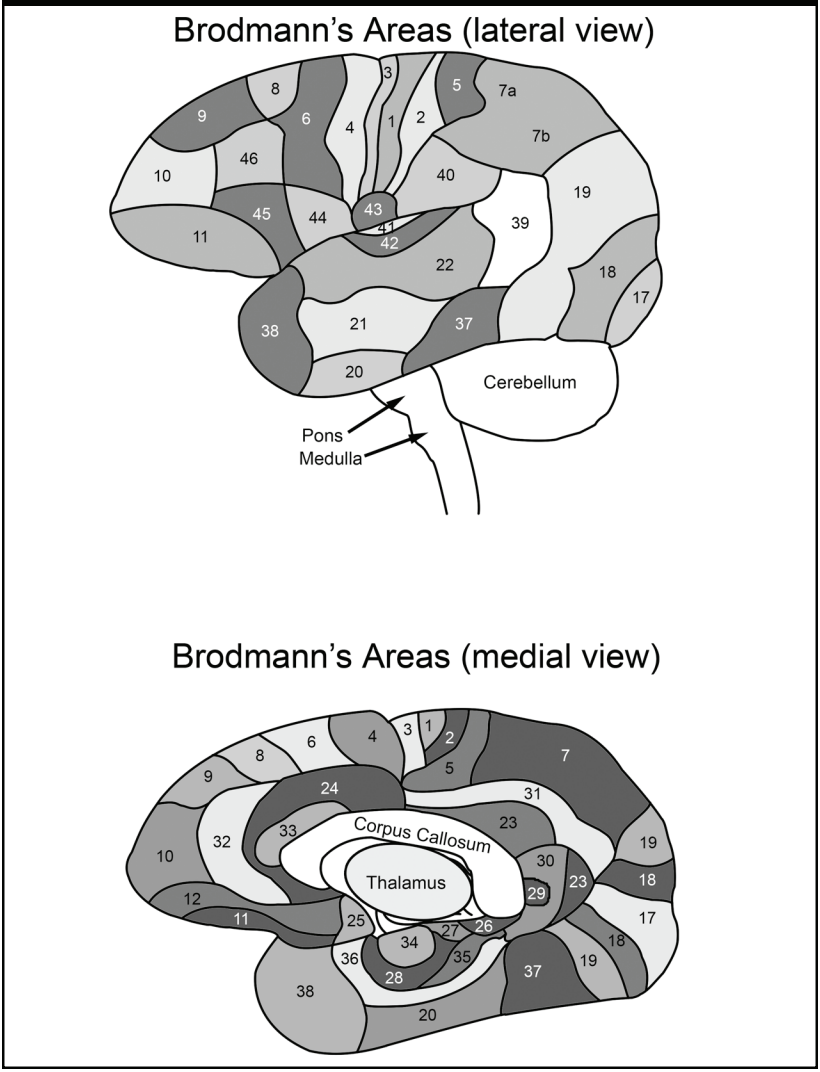
In this lecture we are going to focus on that *cerebral cortex*, and this is this outer mantle of cells. The reason we have lectures devoted to the cortex is because the cortex is believed to be the seat of the mind.

It is the "bark" or outer mantle of gray matter (neurons) covering the cerebral hemispheres of the telencephalon. The cortex appears "wrinkled" and folded because it is compressed in order to fit within the skull; it is estimated that if flattened out, the human cortex would be about 2½ square feet in area. The wrinkles or folds visible on the external surface are referred to as *gyri* (singular = gyrus). The valleys or infoldings of cortical tissue are referred to as *sulci* (singular = sulcus); when a sulcus is deep, it is referred to as a *fissure*.

The cerebral cortex, however, is not a uniform structure. It varies from about 1–4 millimeters in thickness. Different cortical areas vary in terms of *phylogenetic* (evolutionary) age which is reflected in the number of layers. Cortex that is oldest in terms of phylogeny, referred to as archi- (ancient) and paleo- (old) cortex, is made up of fewer cell layers than neo- (new) cortex of more recent evolutionary age. For example, the *hippocampus*, which is an old cortical area involved in learning and memory, has three cell layers. Neocortex is composed of six cell layers and is the most recently evolved cortex. While we also have archi- and paleocortex, most of the human cerebral cortex is made up of neocortex.

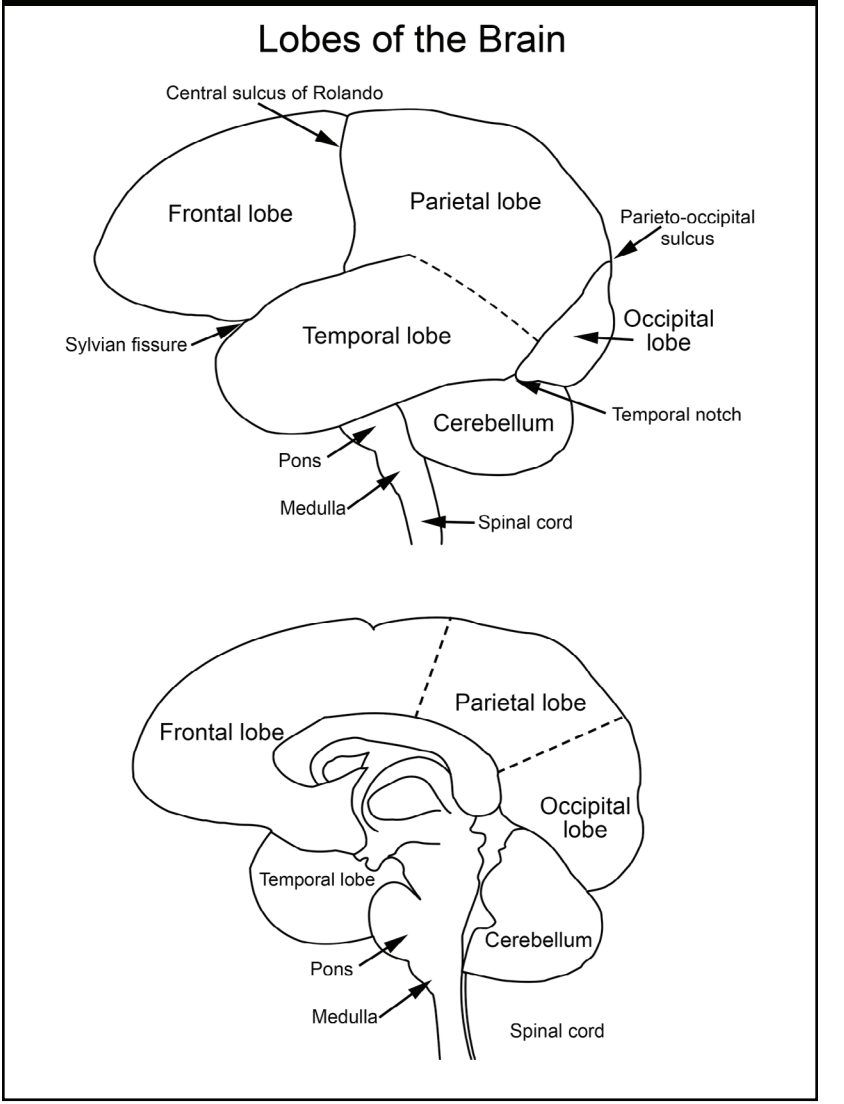
The cortex differs in how the various cell layers are arranged. A number of neuroanatomists around the turn of the century divided the cortex into about 50–200 different areas on the basis of how the neurons were organized into layers (referred to as cytoarchitecture). Figure 5.1 shows the numbering system given to the lateral and medial cortex by Korbinian Brodmann (1868–1918), who divided the cortex into about 50 different areas based on cell arrangement. While we now know that many of these areas can be further subdivided, Brodmann's numbering system is still used in modern neuroscience. Different cortical areas can be referred to by a Brodmann

Figure 5.1



Drawings of Brodmann's areas of the lateral and medial surfaces of the cortex. It will be useful throughout the course to refer back to these drawings as we discuss the function of various cortical areas.

Figure 5.2



The location of the four lobes of the cerebral cortex on the lateral and medial surfaces of the brain.

number, a name, or a Roman numeral; for example, because Area 17 is the first cortical area to receive information about vision, it is also referred to as primary visual cortex or VI; other names given a cortical area may be descriptive (for example, Area 17 is also called "striate" cortex for its striped appearance in the fresh brain).

In addition to a *horizontal organization* the *Brodmann areas* give to the brain, the cortex also has a *vertical organization*. Each 1–2 mm^2 of cortex, extending through the layers, represents a functional unit or module. Thus, the larger surface area of the cortex in humans, which allows for an enormous increase in the number of such functional modules, is believed to underlie the tremendous advantage of our species in processing information as compared to other species.

The cortex can be grossly divided into four lobes by major sulci or fissures (Figure 5.2). Each of the lobes contains a number of important areas; the function of many of these areas will be discussed at greater length in future lectures and will be commented on only briefly here. The *frontal lobe* is demarcated by the *central sulcus of Rolando* and the *Sylvian (lateral) fissure*.

Important areas within the frontal lobe include the precentral gyrus (Area 4), which is immediately rostral to the central sulcus of Rolando; Area 4 is the primary motor cortex, the cortical area responsible for the initiation of a motor movement; neurons in Area 4 give rise to the corticospinal pathway. Areas rostral or anterior to Area 4 include those involved in the planning of a motor movement, and language (left or dominant hemisphere). The most rostral part of the frontal lobe is referred to as the *prefrontal cortex*, which Brodmann divided into sub-areas; different prefrontal areas play a role in a variety of higher cognitive functions including the ability to inhibit behavior and to understand the consequences of one's behavior.

- The *parietal lobe* is bordered anteriorly by the central sulcus of Rolando, posteriorly by the parieto-occipital sulcus. The postcentral gyrus (Areas 3, 1 and 2) lies immediately caudal to the central sulcus of Rolando and represents the primary somatosensory cortex, the

area of cortex involved with the interpretation of sensory input from the body, for example, touch, pain, and temperature. Other parietal lobe areas are involved in associating visual and somatosensory information, and with language (left or dominant hemisphere).

- The *occipital lobe* is located at the posterior pole of the brain; it consists of Brodmann's Areas 17, 18, and 19, and is entirely visual in function; Area 17 is primary visual cortex, the first cortical area involved in vision.

- The *temporal lobe*, which lies inferior to the Sylvian (lateral) fissure, has a large number of functions.

    - For example, Brodmann's Area 41, or primary auditory cortex, is the first cortical area to receive information related to audition or hearing; the surrounding area (Area 22) is responsible for language comprehension (in the left or dominant hemisphere). Other areas in the temporal lobe are involved in visual functions.

    - The temporal lobe is also the location of the *entorhinal cortex* and hippocampus, two structures involved in learning and memory.

Here we have focused on how the cortex is divided, in general, into different lobes and areas. In the next lecture, we will explore how the cortex has been viewed conceptually. ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. Since the cortex is believed to be the seat of the mind, are you surprised that it represents only the outer shell or "bark" of the hemispheres? Since other animals, in particular mammals, have well-developed cortices, do you think they have "minds"? Why or why not?

2. How is the localization of function described in this lecture different from phrenology?

Cortex—Sensory, Motor, and Association Areas

Lecture 6

[W]ithout the brain, the heart wouldn't function. The brain literally controls every organ in the body and controls everything you see, hear, or feel. It allows you to think. All of these things are a function of the cortex.

In the last lecture, we learned that the cerebral cortex is a sheet of neurons about 1–4 millimeters thick covering the two cerebral hemispheres. The cortex can be divided into a number of different areas based on evolutionary age, cytoarchitecture, and function. Brodmann divided the cortex into about 50 areas based primarily on cytoarchitecture. One of the most important of the early discoveries in neuroscience was that many of Brodmann's areas represented functionally distinct areas. Lastly, we learned that the cortex has a vertical/modular organization as well; thus, while the cortex is approximately the same thickness in all species, the increase in surface area in the human brain allows for an increased information processing ability, at least in part, because of the increase in the number of functional modules.

Early neuroanatomists identified the primary areas of the cortex (sensory and motor), but thought that much of the remaining cortex (which they called association cortex) was responsible for higher-order cognitive abilities associated with our species.

While the general classification into sensory, motor, and association cortex is still used in neuroscience, there has been a major paradigm shift in how we view the cortex conceptually, particularly in how association cortex is defined. One of the most important discoveries made within the last 40 years or so is that much of what was previously called association cortex is actually sensory in function; these areas are now referred to as higher-order sensory cortex. For example, in addition to Area 17, many other cortical areas are devoted to vision; in fact, in primates, there may be 30 or more distinct cortical areas within occipital, parietal, and temporal lobes that are devoted to vision.

It has become clear that much of the cortex, even in humans, is devoted to the processing of sensory information (Figure 6.1). When primary and higher-order sensory and motor areas are accounted for, however, there are still identified areas which are either *multimodal* in function (meaning that they process information from more than one sensory system), or are neither sensory nor motor in function; in modern neuroscience, it is these areas which are now referred to as the association areas of the cortex.

Three major association areas are now recognized (Figure 6.1). (1) The prefrontal association cortex is involved in a variety of executive functions, for example, an appreciation of the consequences of one's behavior. (2) The parieto-occipital-temporal association cortex is primarily multimodal. And (3) The limbic association cortex (parts of the frontal and temporal lobes) is involved in the higher-order elaboration of emotion, memory, and other cognitive functions.

In general, any kind of damage to the left hemisphere causes a depression of mood. Whereas, if you have damage to the right hemisphere, you are much more likely to be manic in your behavior, even if it's inappropriate.

As more data, particularly on the human brain, are collected, these definitions may again change. In modern neuroscience, technology is providing noninvasive detailed images of the human brain with such techniques as *functional magnetic resonance imaging* (fMRI), which can show what areas of the brain are active when an individual performs various tasks, providing neuroscience with valuable information about the functional organization of the human cortex.

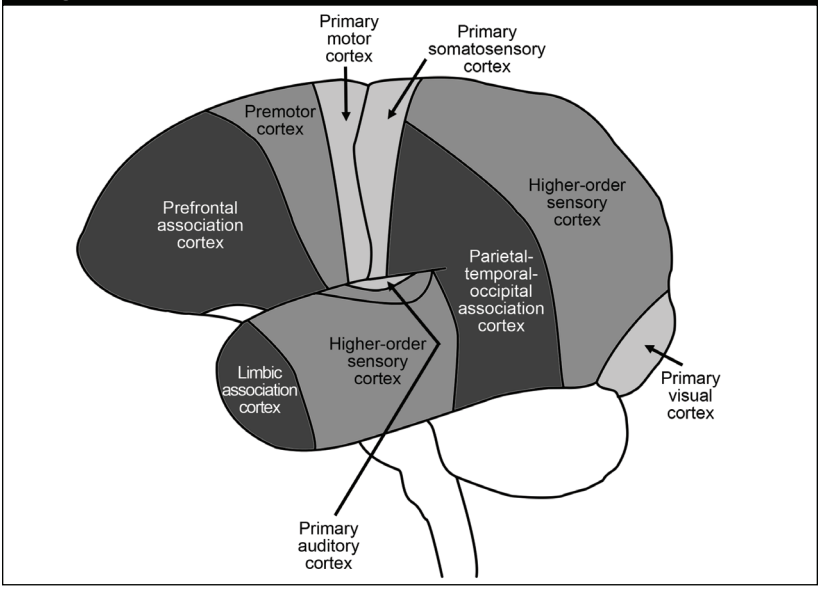
A number of other paradigms have also been challenged by modern neuroscience. For example, historically, it was believed that a few functions, for example language, appeared to be related only to one hemisphere. For other functions, it was generally believed that the hemispheres had similar functions relating to the two sides of the body. We now know that both hemispheres play a role in language, and that the processing of information

is not identical in the two hemispheres, although in general, one hemisphere does process information from or control the opposite side of the body.

For example, it has been long known that each hemisphere is involved in initiating motor movement or in processing sensory information from the opposite (also called *contralateral*) half of the body or world. The motor cortex on the right controls the movement of the left side of the body because the corticospinal tract crosses the midline of the brain before it enters the spinal cord (see Figure 4.1). Likewise, Area 17 or primary visual cortex on the right "sees" the left or contralateral half of visual space.

But modern neuroscience has revealed important, and sometimes subtle, distinctions in cognitive function between the hemispheres; for example, mood is altered differently depending on whether an individual sustains

Figure 6.1



A drawing showing the extent of primary sensory and motor cortex (light areas), higher-order sensory and motor cortex (gray areas), and the three association areas of the cortex (dark areas) recognized in modern neuroscience.

damage to the left or right hemisphere. Neuroscience has also shown us that the hippocampus on the left side of the brain is more involved in being able to remember words and episodes in your life, while your right hippocampus is involved more in spatial memory. Information in the two hemispheres is "coordinated," in part, by projections of the corpus callosum, the 300 million axons that connect a cortical area in one hemisphere with the same area in the other hemisphere.

Essentially, we have two brains in our head. This was discovered in individuals with epilepsy who have the corpus callosum severed or cut to prevent the spread of seizures. This surgery results in an individual with two separate functioning hemispheres; such patients show very little loss of function because their projection pathways are still intact. They have to be tested very carefully to detect any subtle change in function. ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. Even though the cortex can be divided into sensory, motor, and association cortex, no single area brings all of the information together? Yet our experience seems "unified." This is known as the "binding" problem. Why do you suppose it continues to challenge neuroscientists?

2. What do you think about the fact we have, essentially, *two* brains in our heads?

Central Nervous System—Development

Lecture 7

Development in general is just considered a wondrous process, and it really is. The development of the brain is certainly the most complexly-orchestrated event that is going to take place as part of the developmental process.

From a few cells, a human brain will develop the capability of regulating the function of all of the other organs of the body, and also of generating a theory of relativity or appreciating Bach. In this lecture, we will discuss briefly what is known about how the adult subdivisions of the brain arise, and how different cell types found in the brain are generated during development.

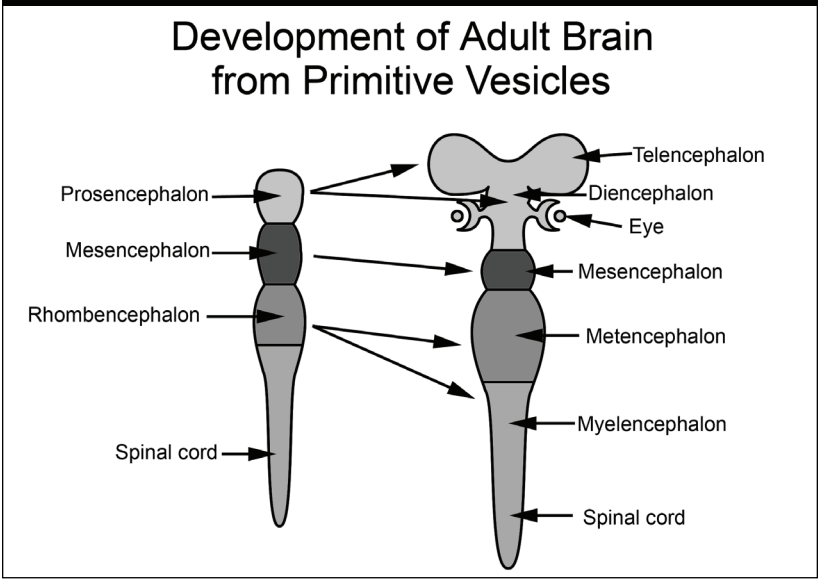
Early in development (at about 18 days of gestation), proliferating cells along the future midline of the back form a structure referred to as the *neural plate*. The neural plate cells proliferate at the edges, folding up to form a long *neural tube*; this process is generally complete by about four weeks of gestation. The inside cavity of the neural tube, formed when the tube closes, will become the ventricular system of the brain, continuing as the *central canal* of the spinal cord in the adult CNS. The neural tube closes along its length except in three places: at its anterior most tip (anterior *neuropore*), at an area about ⅓ of the way down the neural tube (*rhomboid fossa*), and at the posterior most tip (posterior neuropore). The posterior neuropore will close early in development.

The cellular portion of the neural tube surrounding the central cavity actually consists of concentric zones of cells or layers. The cells immediately adjacent to the hole or cavity of the neural tube represent the layer from which neurons and some glial or supporting cells of the CNS (*astrocytes* and *oligodendrocytes*), as well as some other cells, will be generated; this is a zone of *mitotic* activity (cell division); the first *critical period* (a window of time when a specific process takes place) of brain development occurs between 12 and 20 weeks of gestation when the greatest amount of mitotic activity occurs, which is when most neurons are generated.

In the spinal cord, this layer of neurons will differentiate into gray matter which always maintains its position near the central canal. In the brainstem and the telencephalon, some of these neurons stay near the primitive cavity to become nuclei which surround the ventricular system in the adult CNS. Some neurons in the telencephalon, however, will move away from the mitotic zone (*migration*) to form an external sheet of neurons (future cortex); later, white matter will lie in between the neurons near the ventricle that did not migrate and the cortex.

Later in development, after neurons have migrated, their axons will grow out to make contact with other neurons. The first neurons to differentiate fully are the *long-axon neurons* which will make up the associational, commissural, and projection pathways of the brain; these axons make up the white matter of the CNS. The last neurons to differentiate are *short-axon neurons* (*interneurons*) that make local synaptic connections within a

Figure 7.1



A drawing of the three primitive vesicles (left) that become the five subdivisions of the adult human brain (right).

nucleus, but do not project to other areas; these interneurons are intercalated between the input and output of an area. The second critical period of brain development extends from about the third trimester until 2 years of age; this is the period of axon growth and formation of synaptic connections between neurons.

The generation and migration of neurons is significantly greater at the *cephalic* or head end of the neural tube than the posterior end. The head end of the neural tube will differentiate or develop into specialized areas of the brain; this portion shows regional specialization into three primitive vesicles known as the prosencephalon, mesencephalon, and the rhombencephalon, which will develop into the five divisions of the adult brain (Figure 7.1). The prosencephalon will become the forebrain differentiating into the telencephalon and the diencephalon. The neural part of the eye will also develop from part of the diencephalon. The mesencephalon will remain the midbrain in the adult brain. The rhombencephalon will differentiate into the hindbrain consisting of the metencephalon (pons and cerebellum) and the myelencephalon.

The cephalic or head end will continue to develop and expand. Growth of brain structures will effectively close off the early ventricular system of the brain, so that it is entirely internal in the adult brain. The cerebral hemispheres will develop over the anterior neuropore. The cerebellum will develop over the rhomboid fossa.

If all proceeds normally, at birth the CNS consists of more neurons than it will ever have again; shortly after birth, there are regressive events that eliminate both neurons and many of the connections between neurons. After birth, the brain does continue to grow; however, the growth is not due to the addition of neurons, but rather to other processes, for example, the proliferation of *glial cells* and myelination of axons. Even with the regressive events, the adult human brain contains about 100 billion neurons. A number of potentially devastating neurological consequences occurs if any part of this carefully orchestrated developmental sequence is disrupted. ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. What effect on brain development might occur to a fetus if a mother was exposed to toxic substances early in gestation? Late in gestation?

2. What progress has been made in recent decades to improve prenatal care and ensure healthy fetal brain development? What else can be done?

Central Nervous System—Cellular Organization

Lecture 8

Once a cell … decides it's going to become a neuron, or a glial cell, their structure and their function are very, very different. We want to focus on a few of those structural and functional differences between neurons and those two types of glial, or supporting, cells.

Once these cells are committed to becoming either neurons or glia, however, they are very different both in terms of structure and function. Here, we will focus on a few structural and functional differences between neurons and glial cells. The adult CNS consists primarily of neurons and glial cells; there are about 100 billion neurons, and 10–100 times that many glial cells in the brain.

There are at least 150 different types of neurons, making them the most diverse cell type in the body. Neurons are distinguished primarily by their size (about 4–100 microns) and their dendritic arbors. Most neurons are *multipolar* cells, meaning that they have a number of processes emanating from the cell body; the "generic" neuron in Figure 3.1 is a multipolar neuron. In adults, neurons are generally considered nonmitotic cells and thus do not give rise to tumors in the CNS; however, there is a low level of mitosis of neurons in some areas of the adult CNS, a topic we will return to in future lectures.

Glial cells are found in both gray and white matter. There are two major types of glial cells in the brain (astrocytes and oligodendrocytes). The name glia (glue) derives from the historical view that the function of glial cells was to simply hold the brain together, but modern neuroscience has revealed that glia are vital to the normal functioning of the nervous system.

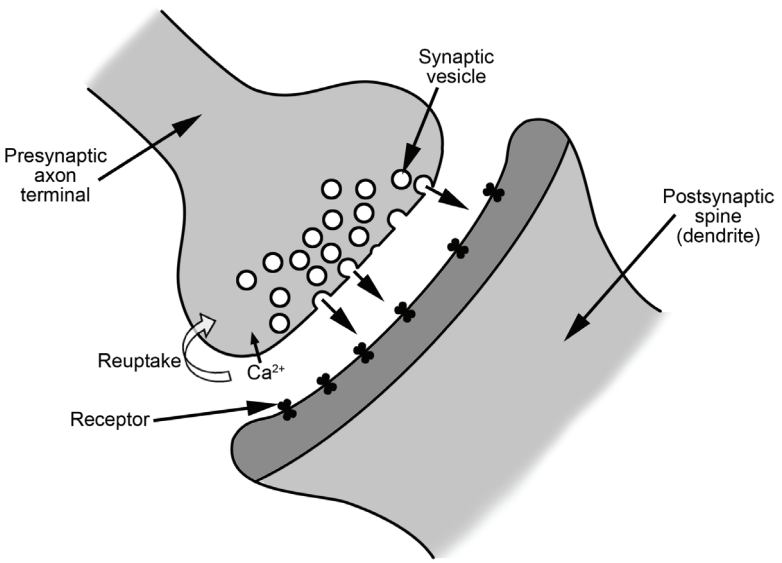
- Astrocytes ("star" cells) are derived from the same precursor cells as neurons. Astrocytes support and guide neurons during development, act as "sinks" for *ions* (charged atoms, for example, potassium [K^+]) involved in neural activity, and remove neuroactive

and potentially neurotoxic substances from the extracellular environment; astrocytes also form scars in the CNS.

- Oligodendrocytes myelinate axons in the CNS.

A number of neurological disorders specifically involve glial cells. Astrocytes and oligodendrocytes remain mitotic throughout life, and thus, give rise to primary brain tumors. The CNS disorder *multiple sclerosis* (multiple "scar-like" areas) is believed to be an autoimmune disorder in which antibodies destroy oligodendrocytes (which myelinate axons) and the myelin sheath surrounding axons; destruction of this myelin sheath alters the ability of the axon to transmit impulses normally.

Figure 8.1



A drawing of a "generic" synapse. In general, axons are presynaptic and dendrites or spines are postsynaptic; the physical separation between these elements is referred to as a synaptic cleft.

Neurons are similar to other cells in the body, except that they are *polarized*. (see Figure 3.1). Polarization refers to the fact that the neuron cell body and dendrites are specialized for receiving information from other neurons, and the axon is a specialized structure for conducting impulses to the dendrites and cell bodies of other neurons. Dendrites and their tiny protrusions called *spines* are true extensions of the cell body surface, greatly increasing the surface area of the cell. As opposed to dendrites, axons are not simply extensions of the cell body surface but are a specialized structure for the *propagation* of an electrical impulse. Generally, each neuron has one axon, although there may be many collaterals or branches, which arise at the breaks or *nodes* between the myelin sheaths (see Figure 4.1).

The junction between the axon of one neuron and (generally) the dendrites or spines of another neuron is referred to as a *synapse* (see Figure 4.1), a term coined by Sir Charles Sherrington (1857–1952) who postulated that there must be a "gap" between neurons in gray matter because conduction was slower than that seen in nerves composed only of axons. Synapses are extremely small and were first seen with electron microscopy in the early 1950s. As shown in Figure 8.1, a synapse is a specialized junction consisting of a *presynaptic* component (generally an axonal ending), a *synaptic cleft* which is the space between the pre- and *postsynaptic* components, and a postsynaptic component (generally a dendrite or spine of another neuron).

The presynaptic component of the synapse has a number of important cellular and molecular structures.

- *Synaptic vesicles* contain chemicals (*neurotransmitters* or *neuromodulators*) which are released by the presynaptic terminal into the synaptic cleft.

- *Transporter* molecules and other proteins may function, for example, in taking a neurotransmitter back up into the presynaptic component to be recycled (referred to as reuptake).

The postsynaptic component of a synapse also has a number of important cellular/molecular structures including postsynaptic receptors

or molecules that bind neurotransmitters and lead to changes in the postsynaptic membrane.

Each of the 100 billion or so neurons in the human brain can make thousands of synapses! A conservative estimate is that there are about 100 trillion synapses in the adult human brain! ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. Isn't it absolutely amazing that thousands and thousands of synapses are firing every time you read a word, think a thought, or plan a move? As you read this question, how many different areas/pathways can you name that are being stimulated?

2. Now that you understand how neurons communicate, discuss why the function of glial cells like astrocytes and oligodendrocytes are so vitally important? Glue, indeed!

Pathways and Synapses

Lecture 9

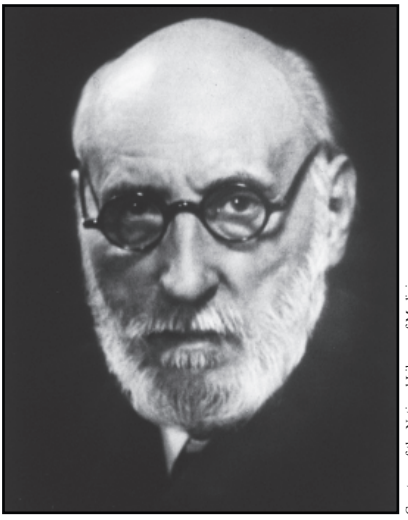
What we want to do in this lecture is to talk about how communication occurs between neurons. We want to understand what the information code is between neurons.

A fundamental principle of neuroscience is that neurons are the structural and functional units of the nervous system. This is known as the *Neuron Doctrine*, a theory that contrasted with the interconnected neural net theory of C. Golgi. Championed by Santiago Ramon y Cajal (1852–1934), a Spanish neuroanatomist, this doctrine established that neurons are the individual cellular units of the nervous system, surrounded by a cellular membrane and separate from other structures like the cells in any other organ in the body. Unlike most cells in the body, however, neurons are specifically designed to receive and to transmit information. Here we review how communication occurs among the 100 billion neurons in the adult brain.

A great advance forward in our understanding of cellular communication in the nervous system came with the discovery that axons generate electricity. The electrical signal is generated at the *axon hillock* and is propagated in an all-or-none fashion, meaning that there is no decrement of the signal as it travels down the axon; the signal "jumps" from node to node in between the myelin wrappings.

The all-or-none electrical signal propagated along axons is known as the *action potential*; all action potentials generated by a single neuron are essentially the same in amplitude. The intensity of a stimulus is encoded by neurons by changing the frequency of the firing of the action potentials; thus, an intense stimulus results in an increased firing rate of action potentials by a given neuron. The quality of the stimulus is the result of the stimulation of various types of neurons; transmission along specific pathways in the brain; and "interpretation" by different areas of the brain, especially the cerebral cortex.

To understand how neurons communicate, it is also important to appreciate the internal and external environment of neurons, and how changes in the distribution of ions (charged atoms) can act as a signaling mechanism for transmitting information in the nervous system. Neurons in the brain are surrounded by an extracellular fluid-filled space in which a number of ions are distributed; the inside of neurons contains intracellular organelles like mitochondria, ions, and a variety of molecules. Ions such as, sodium (Na^+), potassium (K^+), and chloride (Cl^-) are distributed unequally across the neuronal membrane so that in this *resting membrane potential* (when the neuron is not being stimulated), the inside of the cell is more negatively charged than the outside. This charge differential is maintained, in part, by specific molecules within the cell membrane; it is extremely important that ionic concentrations be strictly regulated in the nervous system; abnormalities in these control mechanisms can lead to abnormal electrical discharge or to neuron death. Astrocytes play a critical role in regulating the normal ionic extracellular environment in the CNS.



Courtesy of the National Library of Medicine.

Santiago Ramón y Cajal.

When a neuron is stimulated, the distribution of ions (and thus charge) is altered across the membrane; if the inside of the cell becomes more positively charged, the cell is *depolarized*, and if movement of ions across the neuronal membrane causes the inside of the cell to become more negative, then the cell is said to be *hyperpolarized*. In the resting state, the charge differential is about -70mV. An action potential is generated when a neuron is depolarized to about -55 mV.

Action potentials are generated at the axon hillock of the neuron (see Figure 3.1), and are propagated down the axon as rapid and transient changes in the membrane potential due to the movement of ions only at the breaks or nodes in the myelin sheath along the axon. This is referred to as *saltatory conduction* because the action potential "jumps" from node to node between the myelin sheaths. The velocity of this signal propagation is dependent on myelin, with larger myelinated axons conducting the fastest; unmyelinated axons are the slowest conducting, a fact that helps us understand why a demyelinating disease like multiple sclerosis can cause disability.

So this is how neurons communicate in the nervous system, and the take-home message here that I think is so important is: Neurons don't do very much. They fire or they don't fire.

What happens when the action potential (electrical charge), which is the same amplitude at every place, reaches the axon terminal endings? (See Figure 8.1). At the axonal ending, the action potential causes the presynaptic membrane to open channels allowing an influx of calcium (Ca^{2+}) that sets off a cascade of events resulting in the fusion of synaptic vesicles with the presynaptic membrane and the release of chemicals called neurotransmitters. The neurotransmitter diffuses across the space between the pre- and postsynaptic membranes (synaptic cleft) to interact with *receptors* in the postsynaptic membrane.

What happens in the postsynaptic membrane as the result of the neurotransmitter binding? Neurotransmitter interaction with postsynaptic receptors generates one of two outcomes. It opens channels that are essentially proteins controlling the flow of ions across the neuronal membrane. Or it causes binding with other molecules that ultimately produce changes in the membrane potential in the dendrites or spines.

The changes in the postsynaptic elements are referred to as *synaptic potentials*; they are specifically generated in dendrites and spines. They can also be depolarizing (excitatory) or hyperpolarizing (inhibitory) depending

on the type of postsynaptic receptor involved; it is the sum total of all of the synaptic inputs to a neuron which determines if it will fire an action potential. Unlike action potentials, synaptic potentials are graded and decremental, meaning that their amplitude is not all-or-none. Their amplitude is dependent on the amount of neurotransmitter that is released. Moreover, as the signal is transferred down the neuronal membrane (towards the axon hillock) it degrades or diminishes; thus, excitatory synapses onto distal dendrites have less of an influence on firing the cell than those closer to the axon hillock.

So this is how neurons communicate in the nervous system, and the take-home message here that I think is so important is, note—neurons don't do very much. They fire or they don't fire. Thus, information is transmitted in an electrochemical fashion from neuron to neuron along pathways in the nervous system. Or if it is spontaneously active, it can increase or decrease its firing. That is the information code in the brain. ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science,* edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. Why do you think saltatory conduction in myelinated axons would be faster than conduction in unmyelinated axons?

2. How are depolarization and hyperpolarization related to excitation and inhibition of neurons?

Neurotransmitters

Lecture 10

In this lecture, what I would like to do is elaborate a little bit on the chemical part of this equation. One of the most important things I want you to think about as we are talking in this lecture is that particular neurotransmitters are going to be released by an individual neuron. That neurotransmitter will only bind to a certain postsynaptic receptor, so your neurotransmitter and your receptor have to be matched.

The function of any area of the brain is dependent both on how it is connected via pathways to other areas of the brain, and on the particular neurotransmitter that is used at individual synapses. There is a delicate balance and modulation of excitation and inhibition underlying the normal functioning of the nervous system. Many disorders can be understood in terms of a disruption of this finely orchestrated activity. Thus, damage to a single area of the brain disrupts function not only by removing that area from complicated circuits that underlie a particular function, but also by changing the relative influence of other excitatory and/or inhibitory pathways. In this lecture, we will discuss some of the neurotransmitters used in the CNS, and how synaptic transmission can be modulated.

Neurotransmitters (and neuromodulators) play a critical role in the process of communication that occurs between neurons; they can be divided into a number of classes; here we will mention a few of the major neurotransmitters/modulators used in the CNS that will also be the subject of future lectures in this course.

- Two amino acid neurotransmitters are *glutamate* and *gamma-aminobutyric acid* (GABA). They are the major neurotransmitters in the mammalian CNS.
    - Most long-axon neurons forming projection pathways in the brain use glutamate, which is an excitatory neurotransmitter.

- GABA is also used by long-axon pathways, but it is also a major neurotransmitter used by interneurons. GABA is an inhibitory neurotransmitter.

- *Biogenic amines* (also called *monoamines*) in the CNS include the *catecholamines dopamine* and *norepinephrine*, and the *indolamine* 5-HT (*serotonin*).

  - These neurotransmitters are generally used by neurons localized to small nuclear groups distributed in the brain.

  - While the cell groups utilizing these neurotransmitters are small, their effect is large due to the widespread projections of these neurons.

- Acetylcholine is used as a neurotransmitter by a few cell groups and some interneurons in the brain.

- Peptides are a large, diverse group of molecules that may also act in some cases as hormones.

  - Individual peptides may be specifically localized within particular cell groups involved with a specific function.

  - Enkephalins and endorphins, for example, are peptides that are found in many different areas of the brain involved in processing "pain" in the CNS. They are also found in areas involved in our feelings of well-being.

- Other neurotransmitters include histamine (CNS) and epinephrine (PNS). Approximately 60 or more different neurotransmitters and neuromodulators have been identified.

In reality, the picture is even much more complex. For example, amino acid transmitters like glutamate and GABA can coexist with peptides and be released from the same presynaptic terminals under different conditions; release of other "neuroactive" compounds may also occur at specific

synapses. Moreover, "neuroactive" compounds, including some of the neurotransmitters previously discussed, can also be released at nonsynaptic sites in the brain, influencing the resting membrane potential of neurons in the vicinity, thus altering the effect of the neurotransmitter released during synaptic transmission. Depending on the properties of the postsynaptic receptor, a neurotransmitter can be inhibitory at some synapses, and excitatory at others.

We can talk and move and smile at the same time … because all of these synapses are firing when they should.

Another very important part of this process is that after release, the neurotransmitter in the synaptic cleft and not bound to a postsynaptic receptor must be inactivated. If not inactivated, neurons would continue to fire or otherwise malfunction; this could result in seizures (abnormal neuronal firing) or even the death of neurons.

There is a variety of mechanisms by which the effect of the neurotransmitter is terminated. One is to take the neurotransmitter that has been released back into the presynaptic terminal via autoreceptors present in the presynaptic membrane. Another mechanism is to break down the neurotransmitter by enzymes within the cleft. These breakdown products can then be taken back into the presynaptic terminal to be resynthesized into neurotransmitter for future release. Astrocytes also play a role in removing neuroactive substances (like glutamate) that have been released. This mechanism for the removal of glutamate is especially important because extracellular glutamate can be neurotoxic and lead to the death of neurons.

We have gone into some detail about neurotransmitters because neurotransmitters and neuromodulators are the chemical messengers that signal activity from one neuron to another; thus, synaptic activity is dependent on the mechanisms involving neurotransmitter synthesis, release, binding, and inactivation. We will see in future lectures that all drugs that have an effect in the CNS will influence some part of this overall mechanism.

For example, the drug Prozac is designed to specifically interfere with the reuptake of serotonin, allowing the serotonin that is released at the synapse to have a prolonged effect, increasing feelings of well-being in some individuals. Cocaine operates at serotonergic synapses in the same way Prozac does, but cocaine also influences the dopaminergic system, so it is highly addictive. It is also important to appreciate that when there is damage, either to a nucleus or to a pathway, this will alter the balance of excitation and inhibition in the complex circuits of which those neurons were a part.

Conceptually, we might think of a very simplified model where glutamate and GABA are the major excitatory and inhibitory transmitters. The influence of pathways utilizing these neurotransmitters is then modulated by other neurotransmitters like the monoamines (which is why the latter are often referred to as neuromodulators). Now the function of any part of the brain area is very, very complicated, but it will always strictly regulated. We don't understand everything about how it's regulated, but the reason that we have normal movement, we have normal vision, that we can talk and move and smile at the same time, is because all of these synapses are firing when they should and there is inactivation of neurotransmitter when it needs to occur and firing when it needs to occur.

While this is a gross simplification of very complex process, it is a good first approximation for understanding some of the future topics in this course. ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. What does it mean to say that synaptic transmission is electrochemical?

2. Any drug which influences synaptic transmission in the CNS may alter how you feel. Does this discussion help you understand why a drug like an antihistamine affects you mentally? What other drugs can you think of that alter your feelings?

Stroke

Lecture 11

In this last and final lecture in this segment, I want to use stroke as a clinical example to reinforce what we have covered up to this point and also tell you some very important things about this critical clinical disorder. To understand stroke we need to realize that the brain is very active metabolically.

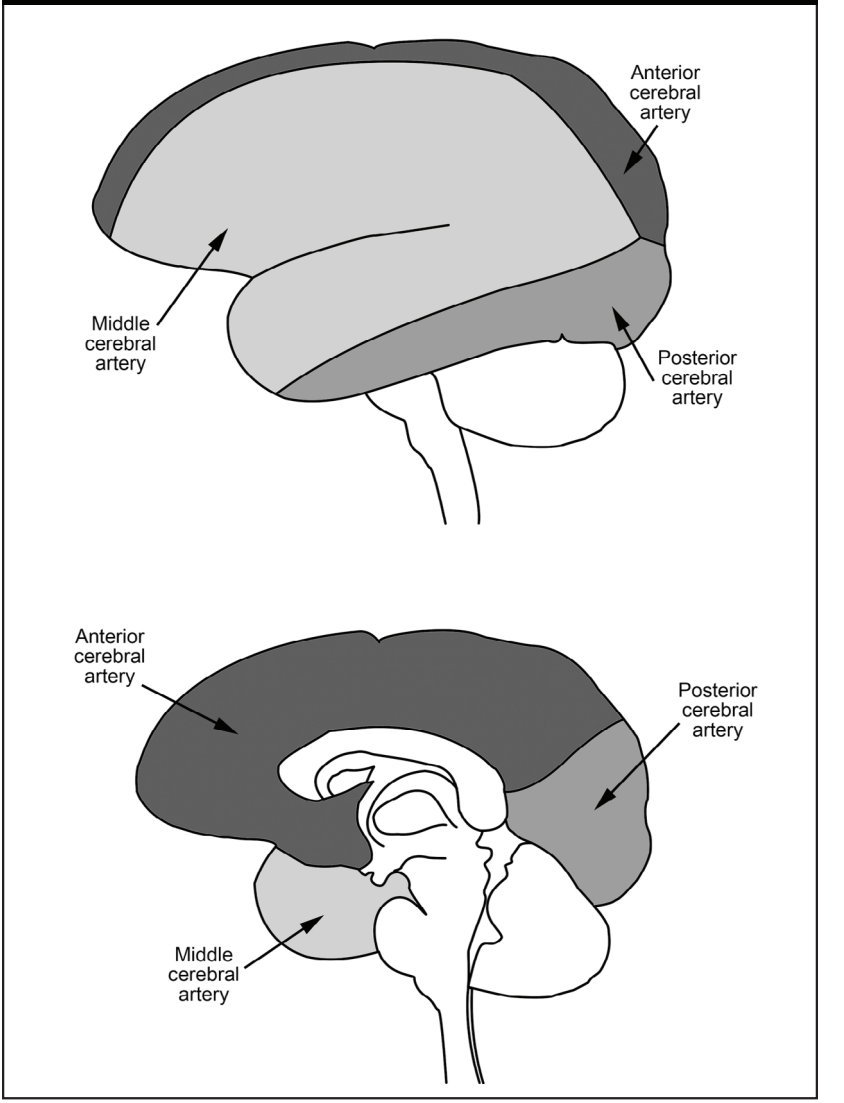
A stroke occurs when the blood supply to an area of the CNS is compromised either by a vessel being occluded or ruptured. Here we will show that understanding the gross organization of the brain and its blood supply allows for the prediction of what functions will be lost or affected after a stroke. We will also review data from studies implicating the neurotransmitter glutamate as a major player in stroke.

It is estimated that although the brain only accounts for a small portion of the total body mass (1–2%), it receives about 20% of the resting cardiac output. The brain also has no ability or very limited ability to store either oxygen or glucose. Neurons die within minutes of being deprived of oxygen, and thus anything that interferes with blood flow can compromise brain function, possibly permanently.

Stroke is the third leading cause of death in the United States and the number one cause of disability. A stroke is essentially a "brain attack," in the sense that we think of compromise of coronary vessels as being a "heart attack." In order to understand stroke and why particular *signs* (what is found upon examination of the patient) and *symptoms* (what the patient complains of) are seen following stroke, we need first to briefly discuss the blood supply to the brain.

While stroke can occur in the spinal cord, it is rare; most strokes involve the brain. The entire blood supply to the brain is from two major arterial (internal carotid and vertebral) systems. The two internal carotids give rise to the anterior and middle cerebral arteries that supply much of the cerebral cortex (Figure 11.1) and deep structures of the hemispheres with blood.

Figure 11.1



Drawings of the lateral and medial parts of the hemisphere to show the blood supply to the cortex.

The two vertebral arteries have branches supplying part of the brainstem and cerebellum with blood. The vertebral arteries join to a single artery (the basilar) that supplies the pons with blood; the basilar divides in its rostral portion to form the two posterior cerebral arteries that supply parts of the cerebral cortex (Figure 11.1), some deep structures of the hemispheres, and some brainstem areas with blood. At the base of the brain, the anterior, middle, and posterior cerebral arteries anastomose, or join, to form a "circle," known as the *circle of Willis* (named after the father of neurology, Thomas Willis).

Strokes occur when any of the vessels supplying any part of the brain are compromised. There are two major kinds of strokes:

- *Hemorrhagic* strokes (15% of strokes) occur when a vessel ruptures and bleeds into the brain.

- *Ischemic* strokes (85% of strokes) occur when the blood supply to some area of the brain is compromised because the vessel is occluded (blocked), either from local processes such as the build up of plaque within the vessel or from a transported clot from somewhere else in the body (for example, a clot of bacteria from the heart).

In general, when the blood supply to an area of the brain is cut off—for whatever reason—the function of that area is compromised or lost. For the following discussion, we limit ourselves to cortical branches of vessels (Figure 11.1). For a review of Brodmann's areas, see Figure 5.1. For example, the primary motor cortex (Area 4) is supplied by branches of both the anterior and middle cerebral arteries, which are themselves branches of the internal carotid artery. The lateral surface of the hemisphere is supplied by the middle cerebral artery. The lateral area of motor cortex on one side controls the movement of the upper part of the body on the other (or contralateral) side. The medial aspect of Area 4, which is involved with movement of the contralateral lower body, is supplied by branches of the anterior cerebral artery; if these specific branches to this area are compromised, then the ability to initiate movement of the contralateral leg will be compromised.

Strokes can involve smaller branches (such as the example just given) or can involve a major branch or artery; for example, the internal carotid gives rise to both the anterior and middle cerebral arteries; thus a stroke of the internal carotid on one side compromises all of the areas supplied on the medial and lateral hemispheres by these two cerebral arteries, and also other areas supplied by the internal carotid.

A stroke involving the posterior cerebral artery, on the other hand, would produce a completely different set of signs and symptoms. A stroke involving cortical branches of the posterior cerebral artery, for example, would produce a loss of vision in the contralateral hemi-field (half) of vision because cortical branches of this artery supply Area 17.

While any type of stroke is potentially serious, they can have quite different outcomes depending on the type of stroke as well as the areas of the brain that are compromised. For example, hemorrhagic strokes are generally more serious than ischemic strokes. In hemorrhagic stroke, the bleed itself or the formation of a blood clot can take up space; because the brain is in a closed compartment, space-occupying lesions (for example, blood clots) can cause the brain to *herniate* or move. Downward movement of the brain through the foramen magnum (where the brain is continuous with the spinal cord) can cause death because of compromise of the reticular formation nuclei located in the medulla which control vital functions like breathing.

Ischemic strokes can also potentially take up space by producing brain swelling (edema); drugs are generally used to help decrease brain edema. Great strides have been made in helping individuals survive ischemic strokes *if treated early*; loss of function and disability from ischemic stroke can occur if blood flow to the area is not restored. Glutamate is implicated in postischemic stroke events that can lead to increased disability.

Ischemia causes neurons to release glutamate into the area surrounding the actual stroke (called the *ischemic penumbra* or *umbrella* area). This places the surrounding neurons at risk if the astrocytes in the area cannot remove this glutamate; if excessive, extracellular glutamate can set off a cascade of events leading to additional neuron death. Sometimes a vessel becomes occluded for a short time and then clears, which is referred to as a *transient*

ischemic attack or TIA; such transient events, however, often signal an impending major stroke. In the event of any sudden onset of neurological signs or symptoms, seek help immediately.

So the take-home message from this lecture—and one which is important—if you ever have a sudden onset of any neurological sign and symptom, meaning anything that anyone listening to this course could attribute to the brain—or to your eye, which is an outgrowth of the brain—seek medical treatment immediately. It doesn't matter whether it got better and it clears or whatever. Seek medical treatment immediately. ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. Did you realize that there were different kinds of stroke? Given what you have learned about the two types of stroke, for what type would a baby aspirin a day be a preventive measure? Why?

2. What are the risk factors for heart attack and stroke? Why would they be the same for both types of attack?

The Visual System—The Eye

Lecture 12

So, here in the first [sensory] lecture we want to talk about the eye and its role in this visual process. Now, far from taking a picture of the external world and sending this picture to the brain, the eye actually transmits very little information.

Of all of the sensory systems, the visual system has undergone the most differentiation or specialization in primates. This allows for increasingly subtle aspects of visual stimulation to be interpreted by our brains. Here we discuss the purpose of the eye, which is to allow an image to be focused onto a thin layer of cells at the back of the eye. Absorption of light by these cells is the first step in a process that will result in an electrical signal being transmitted to the brain. Far from taking a picture of the external world, however, the eye actually transmits information primarily about edges and contrast to the brain. From this limited information, the brain literally constructs the visual world we experience in all of its complexity.

To understand vision or how we "see," we need to begin with a description of the anatomy of the eye (Figure 12.1). The purpose of the eyeball is to focus light rays onto the *retina*, a sheet of neurons at the back of the eye. The function of the *cornea* (the transparent outer layer of cells through which light must pass) and the *lens* (the transparent flexible structure that allows for objects at different distances to be brought into focus) is to bend (refract) the light so it can be focused onto the retina. Disorders of aging, for example, *cataracts* (clouding of the lens) and *presbyopia* (loss of the flexibility of the lens) thus affect the transmission and refraction powers of the eye.

The *pupil* acts as a variable aperture (as in a camera), letting in more light under low light conditions, and closing down to protect the retina under bright light conditions. The lens reverses and inverts images, but your brain will right that image appropriately.

The retina (a multilayered sheet of neurons located at the back of the eyeball) is derived from the diencephalon in development; it is a part of

the CNS located on the external part of the body and therefore needs to be protected. Anything that would damage this neural structure (for example, *glaucoma*, which is due to an abnormally high pressure in the eye) can cause irreversible blindness.

- The *macula*, or *macula lutea*, is the central area of the retina where the light is focused; the *fovea*, or *fovea centralis*, is in the very center of the macula and is responsible for color and high visual acuity vision. It allows us the ability to see and interpret individual forms; we move our eyes and head so that the line-of-sight will fall onto the fovea.

- The *optic disc* is the area of the eye where axons of *retinal ganglion cells* (RGCs) leave the eye (as the *optic nerve*) to project to the brain. This area of your retina is actually "blind," but the brain fills in the part of the visual field that is missing.

The neural retina is made up of five types of neurons distributed in a number of layers. At the very back of the retina, light is absorbed by two types of photoreceptors.

- *Rods* (120 million) are photoreceptors specialized for vision under low light conditions and are most numerous in the peripheral areas of the retina; the photopigment within rods (rhodopsin), can absorb a single photon of light making rods exquisitely sensitive.

- *Cones* (6 million) are photoreceptors responsible for vision under high light conditions; they are concentrated in macular/foveal regions and are responsible for color and high-acuity vision (referred to as form or discriminative vision).

The absorption of light by rods and cones causes changes in the photoreceptors that result in the stimulation of a second neuron in the chain (*bipolar neurons*); the latter are interneurons in the retina, located between the photoreceptors (rods and cones) and RGCs. Many rods converge onto a single bipolar cell; this convergence, in conjunction with the ability of rhodopsin to absorb a single photon of light, accounts for the tremendous sensitivity of rods. In

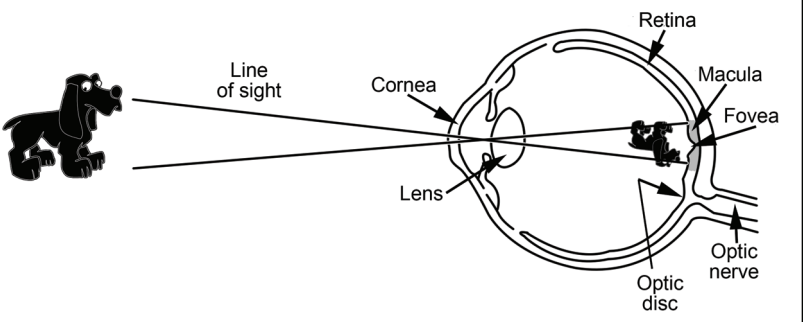
the fovea, there is a 1:1:1 relationship (a vertical organization) between cones, bipolar cells, and RGCs resulting in less sensitivity, but greater discrimination. In summary, it is the fovea that is specialized for color and form vision and accounts for the ability to discriminate fine details.

There are two other interneurons in the retina called *amacrine* cells and horizontal cells, which integrate information across the retina and play a role primarily in sharpening of the images. Shown schematically in Figure 12.2, the retina has a vertical organization (photoreceptor-bipolar-RGCs) and a horizontal organization (horizontal and amacrine cells). Horizontal and amacrine cells "sharpen" the information transmitted vertically.

RGCs (1 million) are the only neurons to project outside of the eye; their axons project via the optic nerve/tract to the *lateral geniculate nucleus* (LGN) of the thalamus; the LGN then projects to the visual cortex (Area 17), which begins to create the subjective experience that we call "seeing" (Figure 12.3).

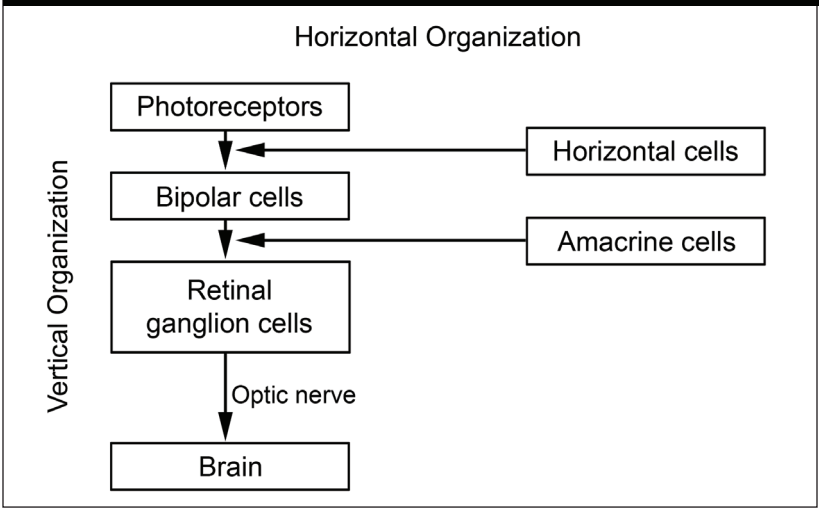
The eye does not transmit a picture of the world to the brain. When we think in terms of vision, we need to consider what information is transmitted to the brain. Neurons in the retina are spontaneously active, which means they can only increase or decrease firing with stimulation; what is transmitted to the

Figure 12.1



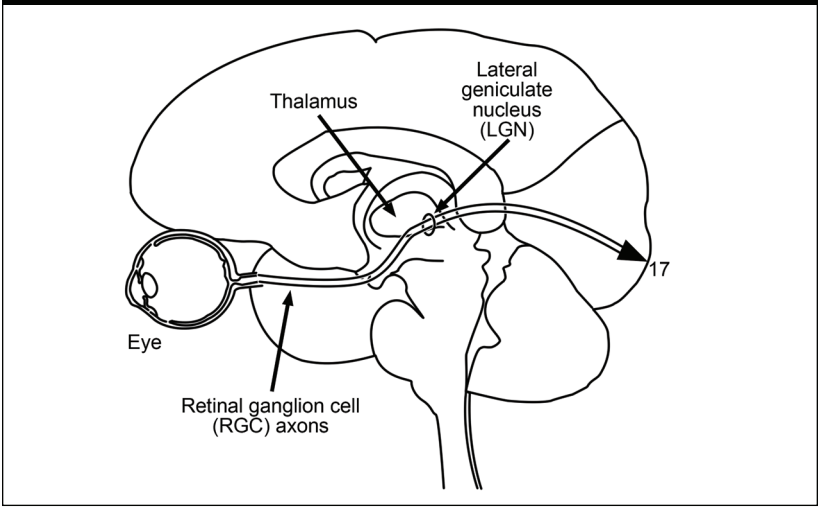
A drawing of the major structures of the eye.

Figure 12.2



A schematic drawing of the vertical and horizontal organization of the retina.

Figure 12.3



A drawing of the RGC projection to the brain.

brain is information about "change," this is due, in part, to properties of the RGCs themselves.

RGCs are specialized to transmit specific types of information; different types of RGCs are distributed nonuniformly across the retina; thus, information is transmitted to the brain in multiple parallel pathways. RGCs representing the macular or foveal part of the retina transmit information about form (contrast and edges) and color. The RGCs in the peripheral retina transmit information primarily about change that signals movement.

Much information coming into the eye is never transmitted to the brain. After all, there are 120 million rods, 6 million cones, but only 1 million RGCs. It is estimated that RGCs, by increasing or decreasing their firing in response to *changing* stimulation of the retina, transmit 1 billion bits or pieces of information each second to the brain.

In the human visual system we care about change, contrast, and color. But if you were to look at the eye across the vertebrate kingdom, you would see specializations in the structure related to the niche that that animal occupies. ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. What parts of the eye are similar to a camera?

2. Did you know that the eye is the only part of the body in which blood vessels and CNS tissue can be observed directly? What might be the advantages and the disadvantages of this fact?

The Visual System—The Cortex

Lecture 13

In this lecture what we want to focus on are the projections of the retina to structures that are going to eventually project to the cortex. The reason for this is because the cortex is the seat of the mind, and so we are interested in the area of the brain that forms percepts that ultimately result in our having a subjective experience of vision.

Different classes of RGCs transmit information to the brain about form, color, and motion using multiple parallel pathways. RGC axons leave the eye at the optic disc, form the optic nerve and tract, and then project to the LGN. We have frontally placed eyes, so with both eyes open, we have a large binocular portion to our *visual field*. The part of the visual field seen with one eye is called monocular. Parts of each eye project to both sides of the brain (Figure 13.1), so that each hemisphere processes information from the contralateral (opposite) half of the visual field; information from each eye, however, is kept separate in visual structures, as is information about form, motion, and color.

The projection of the retina is such that each point on the retina is represented in a point-to-point way in the LGN (and other visual structures, although these "maps" may be organized differently). The retinotopic or visiotopic map is an orderly representation of the point-to-point projection of RGCs. The map may be distorted, however. For example, while the fovea and macular areas are small within the retina, more tissue in the LGN is devoted to the central compared to peripheral retina. Thus, more tissue is devoted to an analysis of form and color.

Neurons of the LGN project to the primary visual cortex or Area 17. Nearly a third of Area 17 is devoted exclusively to the foveal or macular region, so again, the map is distorted because we are foveate animals. Some of the neurons in Area 17 (VI) project to the surrounding Area 18 (VII).

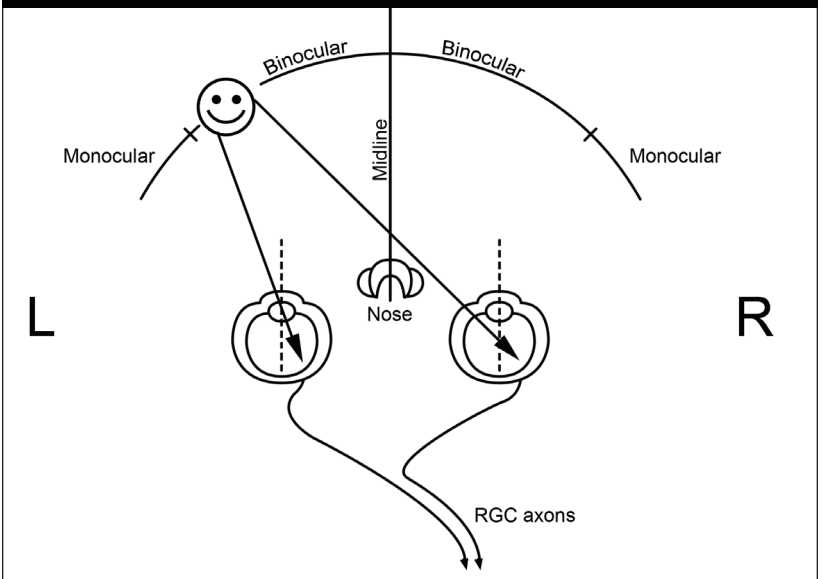
From Areas 17 (VI) and/or 18 (VII), information is transmitted to higher-order sensory cortex (see Figure 6.1); in the cortex, there are two major streams of projections (Figure 13.2).

A dorsal stream analyzes properties of the stimulus related to *where* a structure is located in visual space.

A ventral stream analyzes *what* a stimulus is.

There may be more than 30 visual cortical areas in the human brain, each one processing information about the where and what of vision; each area processes some specific aspect of the visual signal. The pathway involved in color vision is part of the ventral stream; neurons in Area 17 project to

Figure 13.1

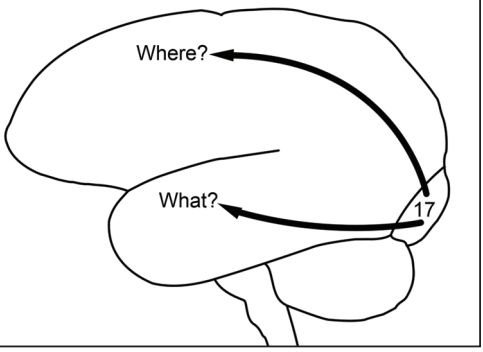


A drawing showing why images in one half of the visual field are processed by the contralateral side of the brain. Monocular and binocular refer to what can be seen by only one eye or both eyes, respectively, with the individual looking straight ahead.

18, which then projects to an area in the temporal lobe known as V4; V4 is one of the major areas of the cortex underlying color vision.

How do we know that "seeing" is a construct created by the brain? Many examples can be given, from the fact that the brain "fills in" the blind spot in the retina (where the optic nerve leaves the retina), to visual illusions such as "ambiguous" figures that can be interpreted in different ways by the brain even though the stimulation on the retina is the same.

Figure 13.2

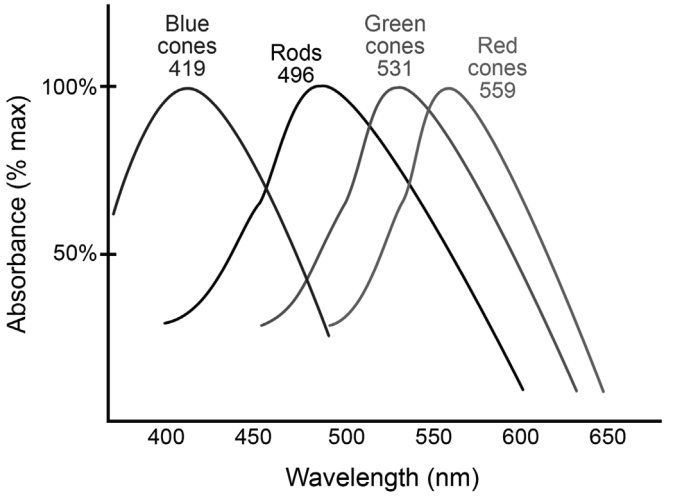


A drawing showing the two main streams of visual information, one dorsal for determining "where" something is and one ventral for determining "what" something is.

Here we will use color vision, and in particular, our perception of the color blue, to illustrate that what we "see" is a construct created by the brain. Color vision requires two types of photoreceptors that respond to different parts of the visual spectrum of light. In human color vision, there are three types of cones (each with a different photopigment or iodopsin) with absorbance spectra as shown in Figure 13.3; moreover, these cones are not distributed equally in the retina. Short-wavelength light ("blue" light) degrades images, and thus the retina has yellow pigment in the central retina (where acuity is important) that absorbs short-wavelength light; moreover, there are no "blue" cones in the central retina.

How then can we look directly at something and see it as blue? It is because the brain compares the relative incoming signals from all of the cones, and uses the absence of firing of "blue" cones, combined with the relative change in the firings of the other cones, to create the experience (percept) of blue. All color perception is the consequence of the brain's

Figure 13.3



A graph showing the absorbance spectra of rods and the three types of cones.

interpretation of the relative firing patterns of the three types of cones; color is what we experience privately and subjectively, it is not a property of objects—it is a construct of the brain.

So what is the purpose of color? Surely not so we can appreciate the beauty of a sunset! Color greatly enhances contrast (which the brain does care about!); it is estimated that we can discriminate about 500 variations in brightness, but about 6 million hues of color. In general women have better color vision than men, so not only does learning play a role in our ability to distinguish between different colors, but gender may play a role as well. ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. It is said that animals like cats are color "blind"; in fact, cats do have two types of photoreceptors with different absorbance spectra which should allow for color vision. Apparently the animal does not *USE* this information, at least not in any way that has been determined. What visual capabilities do you suppose we humans have that we do not use?

2. Why does the macular area of the retina have a disproportionate amount of cortex devoted to it?

The Auditory System

Lecture 14

Now for the auditory system I won't be going into as much detail as I did in the visual system. What we want to do is to get a general idea as to how information is processed in the sensory system. We will also want to look at in what ways that vision and audition are similar, at least on a neurobiological level.

Hearing, like seeing, is a construction of the brain. In this system, transmission of pressure waves in the air causes the vibration of membranes and stimulation of cells in the ear. These cells then transmit electrical signals to the brain over complex pathways, eventually stimulating auditory areas of the cortex. The latter stimulation is experienced as sound. Also, as in vision, where particular patterns of firing of different types of cells are experienced as "colors," particular "sounds" can be mapped to meaning. Here we look briefly at the anatomy involved in audition, and then move to the significance of audition in terms of our experience of hearing sound. Throughout this lecture, we will try to draw parallels between seeing and hearing—two of the most important ways we obtain information about the external world.

The peripheral auditory apparatus can be divided into three areas: the external, middle, and inner ear. Sounds waves are funneled into the external ear canal where they cause vibration of the *ear drum* (*tympanic membrane*); the eardrum separates the external and middle ear. The vibration of the ear drum is transmitted across the middle ear cavity by a chain of three tiny bones which efficiently focus the acoustic energy in the air into the dense fluid medium of the inner ear. This process improves the ability to detect faint airborne vibrations by more than 30 times. The inner ear contains the *cochlea*, a coiled, fluid-filled, multi-chambered, membranous structure; the inner ear also contains structures related to the vestibular system.

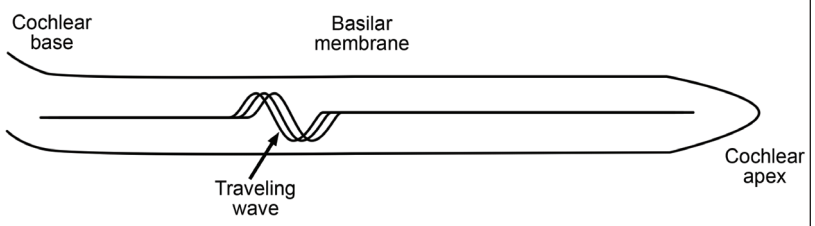
The *organ of Corti* is the part of the cochlea that contains the receptors for the auditory system; the transmission of pressure into the inner ear sets up a traveling "wave" along the basilar membrane in the organ of Corti

(Figure 14.1). The vibration of the basilar membrane causes excitation of auditory receptors (called "hair cells"); these hair cells are comparable to the photoreceptors of the retina. Cochlear neurons are in the PNS. Each of these neurons has a peripheral process which contacts hair cells in the cochlea, and a central process which projects into the brain As in the visual system, neurons throughout the auditory pathway are spontaneously active, and thus either increase or decrease their firing in response to stimulation.

Vibration of the basilar membrane begins at the base of the cochlea and travels along the membrane with increasing magnitude to a point of maximum vibration; impulses reaching the brain from the place of maximal stimulation will be interpreted as a particular *pitch* of sound.

Just as there is a retinotopic organization or map in visual structures, there is a tonotopic map in brain structures in the auditory system. This tonotopic map is a map of vibrations of the basilar membrane or map of pitches, with high-frequency vibrations stimulating the base of the basilar membrane and low-frequency vibrations stimulating the apex. Just as the fovea has a disproportionately large representation in visual structures, more neural space in auditory structures is involved in the processing of sounds found in human speech. *Presbycusis* (comparable to presbyopia in the visual system) is a loss of hearing at the higher frequencies that occurs from the loss of flexibility of the basilar membrane due to aging. Hair cells are also

Figure 14.1



A drawing of the basilar membrane in the organ of Corti of the cochlea. Vibration of the basilar membrane stimulates auditory receptors. The place of maximal stimulation will be interpreted by the brain as a particular "pitch" of sound.

extremely sensitive to loud sounds—so hearing loss as we age is also due to noise trauma, both acute and chronic. There are projections from the brain back to the ear that act to dampen the transmission of loud sounds, to protect our auditory receptors. Since they are neurons, the receptor cells cannot be replaced if they are damaged.

Processes of cochlear neurons make up the auditory nerve which projects into the brain to synapse onto neurons in the medulla (cochlear nuclei); low and high frequency sounds are still kept segregated, as is the information coming into each ear (comparable again to the visual system). Neurons from the cochlear nuclei then project to a number of other auditory structures in both hemispheres; this bilaterality in the projections has the consequence that unilateral or one-sided damage to neurons in these structures does not produce deafness.

For the very first time ever, we can actually answer a question posed by old-time philosophers, and that question was, if a tree falls in the forest and there is no one there to hear it, does it make sound? And the answer is no.

Ultimately, neurons of various auditory structures in the brain will project to the *medial geniculate nucleus* (MGN) of the thalamus (comparable to the LGN for vision). The MGN projects to primary auditory cortex (Area 41) of the temporal lobe; surrounding Area 41 are higher-order auditory areas that are responsible for our "hearing" of sounds and interpreting sound in a meaningful way.

Now let's talk about "hearing" which, like "seeing," is a construct of the brain. First, we can answer the age-old question asked by ancient philosophers. "If a tree falls in the forest and there is no one there to hear it, does it make sound?" The answer is no, sound is what our brain creates from vibrations that affect receptors, which then transmit this information to the brain.

Humans are meaning-making organisms—we don't just "hear" sounds—we interpret sounds and apply meaning to the experience. Language, which is also the topic of one of our future lectures, is the most obvious example.

We cannot hear speech in a language we understand without interpreting the meaning of the words; this meaning has been mapped onto the sounds in our brains. Likewise, when you hear a language you don't understand, it just sounds like noise. ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. When we are having difficulty locating the source of a sound, we turn our heads. Given what you have learned in this chapter, why do you think we do this?

2. Which is most precious to you, sight or hearing? Why?

The Somatosensory System

Lecture 15

Now, in contrast to the auditory and visual systems, our *somatosensory system* is a specific system which is going to convey information that the brain is going to use to form percepts that are related to touch and other sensations which are within the distance of our body, and also information about our bodies themselves.

Our visual and auditory systems allow us to obtain information about a world outside of our bodies and at a distance. This information is used to create mental percepts which we interpret as "seeing" and "hearing" and are the principal ways we obtain information about the physical world in which we live. In contrast, the *somatosensory system* gives us information not only about the immediate external world, but also about our own bodies. Parallel pathways transmit information from receptors in our skin and joints (and other areas) that we experience as the senses of touch, *proprioception* (awareness of where our limbs are), pain, and temperature. In this lecture, we will review briefly the an atomy and function of this sensory system, and compare and contrast it with the visual and auditory systems.

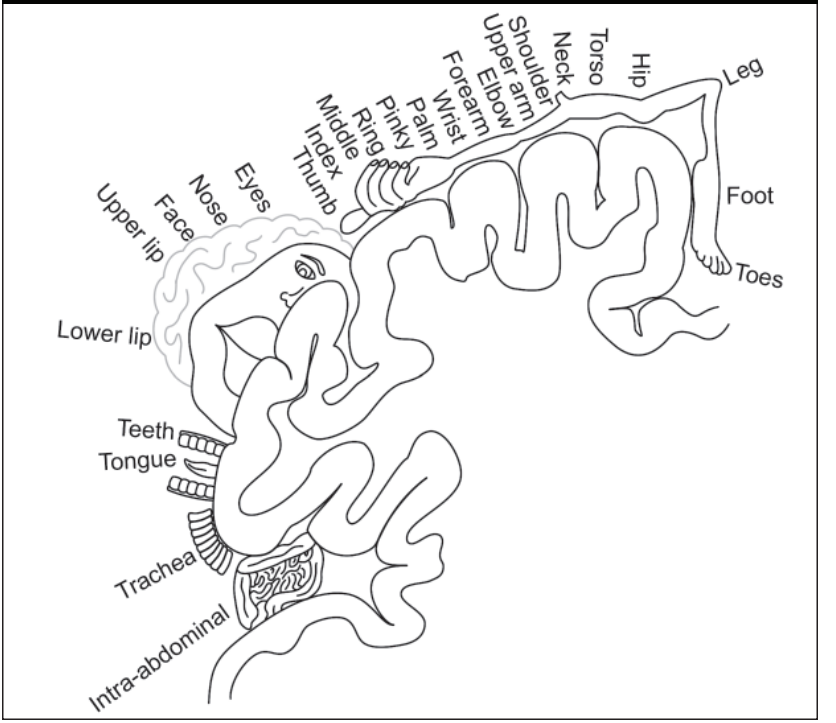
Static proprioception is an awareness of where our limbs are when they are at rest; dynamic proprioception is an awareness of where our limbs are when they are moving. Combined with other information, for example from the visual system, our brain will also form constructs about personal and extra-personal space. It is this system which will also provide the feedback to our brains about the state of our bodies.

There are differences between the visual and auditory systems and the somatosensory system. In the somatosensory system, receptors for the various sensations are localized throughout the body, rather than in a single area (for example, the eye or ear). Neurons in the somatosensory system are not spontaneously active, so that in this system it is not the relative firing which is important (in general) but the threshold of stimulation that provides information to the brain.

In the somatosensory system, the sensations of pain, temperature, touch, and proprioception depend on the type of receptor that is stimulated, the pathways carrying the various types of information to the brain, and the interpretation by the brain (cortex). For example, our experience of pain can result from the stimulation of free nerve endings in the skin; pain is a *nociceptive* sense, transmitting information to the brain about potentially damaging stimulation of some part of the body.

Our sense of *discriminative* or *fine touch*, on the other hand, results from the stimulation of a different type of receptor. Receptors called Meissner's corpuscles are concentrated in the tips of the fingers, soles of the feet, and

Figure 15.1



The somatotopic representation of the body in lateral and medial areas of primary somatosensory cortex.

external genitalia. They are exquisitely sensitive to touch. Other receptors act differently depending on their location in the body. Receptors called Pacinian corpuscles can act as a touch receptor if located in the skin and a proprioceptor if located in a joint.

Our somatosensory system is organized differently in different animals. It turns out that one of the best studied of all these systems is going to be animals that actually use their whiskers as somatosensory organs.

Just as with the other sensory systems, information from the various submodalities is kept separate and travels to the brain in parallel pathways. For example, pain is carried by a phylogenetically old pathway; discriminative touch, on the other hand, is carried by a different and phylogenetically newer pathway. Eventually, all of the separate parallel pathways transmitting information about sensation in the body synapse in a thalamic nucleus called the ventral posterior nucleus. The ventral posterior nucleus will then project to primary somatosensory cortex (Areas 3, 1, and 2); the latter areas will then project to higher-order somatosensory cortex involved in forming the percepts we experience as pain and temperature, touch, and proprioception.

Just as there were retinotopic maps in visual structures, and tonotopic maps in auditory structures, somatosensory structures have an orderly representation of the body surface referred to as a *somatotopic* map. In the primary somatosensory cortex, the face is represented laterally and the leg medially (Figure 15.1). Also, just as with the other sensory systems, the map may be distorted; in the somatosensory cortex of humans, for example, a greater amount of cortex is devoted to information coming from the mouth and the fingers, areas extremely discriminative and sensitive to touch.

We will use two examples to illustrate the importance of the somatosensory system. Pain is an extremely important sense in all mammals. Pain is different from all of the other senses (which require cortex for the conscious appreciation or formation of a percept) in that it can be felt or experienced at the level of the thalamus, but cortex is required for the precise quality and

localization of pain. Unlike the other submodalities of the somatosensory system, there are descending pathways in the brain that can actually block or gate the transmission of pain information at the spinal cord—so the information is never sent on to the brain. Pain is important even at a subconscious level; small movements as we are sitting, for example, prevent tissue damage at the points of pressure; bed sores form at these points of pressure in bedridden individuals, the elderly (where pain thresholds are higher), and in individuals suffering spinal cord injuries (in whom information about pain is not being transmitted to the brain).

In humans, pain has an emotional component which can be disassociated from the pain itself. For example, after prefrontal *lobotomies* (removal of the lobe) or *leukotomies* (undercutting axons going to the area) were performed on patients in intractable pain, it was found that the individuals felt the pain just as they did before surgery, they simply "didn't care" anymore. The emotional component of the experience had been dissociated from the pain itself.

Our second example relates to the finding that in some animals, whiskers act as discriminative somatosensory "organs" allowing the animal to navigate without seeing well, such as in the dark. Thus, whereas in humans more somatosensory cortex is devoted to information coming from the mouth and fingertips, in rodents, a disproportionate amount of cortex is devoted to an analysis of the information coming in from deflection of each individual whisker. We are highly visual animals; our primary way of experiencing the world is through vision. The rat, on the other hand, experiences a different and very "tactile" world. Other animals, with systems adapted to different niches, experience different "worlds." ■

Suggested Reading

T. Nagel, "What Is It Like to Be a Bat?" in *The Mind's I,* pp. 391–414.

Questions to Consider

1. In what ways are the visual, auditory, and somatosensory systems similar? In what ways are they different?

2. It should be clear at this point that what areas of the brain are highly differentiated in various mammals depends, in part, on the animal's niche. Would you be able to venture a very good guess about what sensory areas of the brain are exceptionally well-developed, in say, a dog? A bat? A dolphin? An owl? A snake?

Agnosias

Lecture 16

In this lecture we want to review information that's gained from clinical cases that's going to contribute to our understanding of how the brain forms these individual percepts which are related to sensory systems. Now we are going to focus primarily on examples [of *visual agnosias*] where there has been damage to cortical areas which has caused the loss of the percept itself.

Visual agnosias is when an individual who can see loses some specific "knowledge" as to what an object is or some other aspect of the mental representation essential for normal vision. We will review other fairly rare clinical conditions which inform us about how the brain creates an internal construct about our own bodies which we appear to inhabit, and which we interpret as part of our "selves," separate from an external world.

Animal research has provided us with a great deal of information about how the brain is organized; what we know about the higher-order function of the brain, however, has come largely from an analysis of clinical cases in humans. Here we will review some clinical examples which underscore that seeing, hearing, and feeling are percepts created by the brain. In later chapters, we will return to an analysis of some of these cases to take a closer look at what appears to be "lost" in patients with *lesions* or damage to cortical areas; such an analysis is providing insight into the very nature of consciousness. In the following discussion, it is easiest to explain and understand if it is assumed that the lesions (brain damage) are bilateral.

Damage to Area 17 or primary visual cortex results in *cortical blindness*, while damage to *extrastriate cortex* (any visual areas in occipital, parietal, or temporal lobes outside of Area 17) can also lead to a variety of more complex visual problems. An individual with visual object agnosia (an agnosia refers to a "loss of knowledge") can see (Area 17 is intact), but other higher-order areas (such as Area 19) are damaged; when shown a common object (like a pen), the individual can see it, but cannot identify what the object is by sight.

Similar object agnosias can occur for the other sensory systems. For example, somatosensory object agnosia is a disorder where the individual can feel normally, but loses the ability to recognize an object on the basis of touch. If individuals with object agnosias are allowed to use other intact sensory systems, they can identify the objects.

So initially it's probably true that the child does not see themselves as separate from their mother or from the external world. This is something that develops.

There are other types of agnosias, for example in the visual system, which reflect that different higher-order cortical areas play a critical role in the construction of our experience. For example, lesions of the medial-temporal junction between the occipital and temporal lobes can produce a *motion agnosia*, in which an individual can no longer perceive motion. *Color agnosias* of various types can occur following cortical lesions of higher-order visual areas; for example, lesions of specific areas can produce an agnosia in which the individual, although able to discriminate between different wavelengths of light, does not perceive "color" (this is to be contrasted with true color blindness in which an individual is lacking a particular type of cone, for example; the latter individual will not be able to distinguish particular wavelengths).

Prosopagnosia is a higher-order visual area disorder which results from damage to Areas 20 and 21 of the temporal lobe, areas of the brain that allow us to recognize faces. An individual with this disorder cannot identify individual faces, even though they can see normally and are able to describe a given face in great detail. Such individuals cannot recognize their own face in a mirror.

One of the most fascinating disorders involving higher-order cortex occurs in individuals with unilateral damage to the right parietal cortex (parts of Areas 5 and 7). Such patients experience *contralateral* (left-sided) *neglect*. In this disorder, the left side of the body is not recognized as part of the individual, and the left side of the visual world is neglected; there appears

to be a loss of awareness of the contralateral body and world (personal and extrapersonal space).

Lesions of the left parietal cortex, however, do not produce contralateral (in this case right-sided) neglect; this indicates that these areas on the two sides of the brain are processing information about the body and its relationship to space in different ways. The current hypothesis is the right posterior parietal cortex contains a representation of both the right and the left sides of the body and the visual world, whereas the left parietal cortex has only a representation of the contralateral or right half of the body and visual world. The distinction between our own bodies and the world outside of our bodies is believed to be one of the first constructs created by the brain in infants. ■

Suggested Reading

Any books by Oliver Sacks or Harold Klawans are highly recommended. Both present very compelling and interesting stories about patients with a variety of higher-order disorders, including agnosias and neglect.

Questions to Consider

1. Before this lecture, did you consider that even your ability to perceive parts of your own body as being part of "you" was actually a construction of your brain? In what other ways do we conceive of ourselves as unique individuals?

2. Our ability to differentiate any objects can be lost with the appropriate brain lesion. There are reports in the clinical literature, for example, where an individual has specifically lost the ability to distinguish between vegetables or between different animals using sight – without a deficit in vision per se, or any deficit in the ability to describe various members of these classes. How might such a person find ways to distinguish between members of these classes?

The Motor System—Voluntary Movement

Lecture 17

Motor behavior is going to be initiated in the cortex, and now both systems are going to go down to affect behavior in the body. Here we want to talk about how action occurs as the result of activation of particular cortical areas.

We both experience and move in the world. Sensory perception leads to internal processes which allow our brains to formulate both thought and plans about action. Here we discuss briefly how action occurs as the result of activation of areas of the cortex involved in motor planning and initiation (the "pyramidal" system). How other "extrapyramidal" structures critical to motor behavior participate in making a movement will also be discussed.

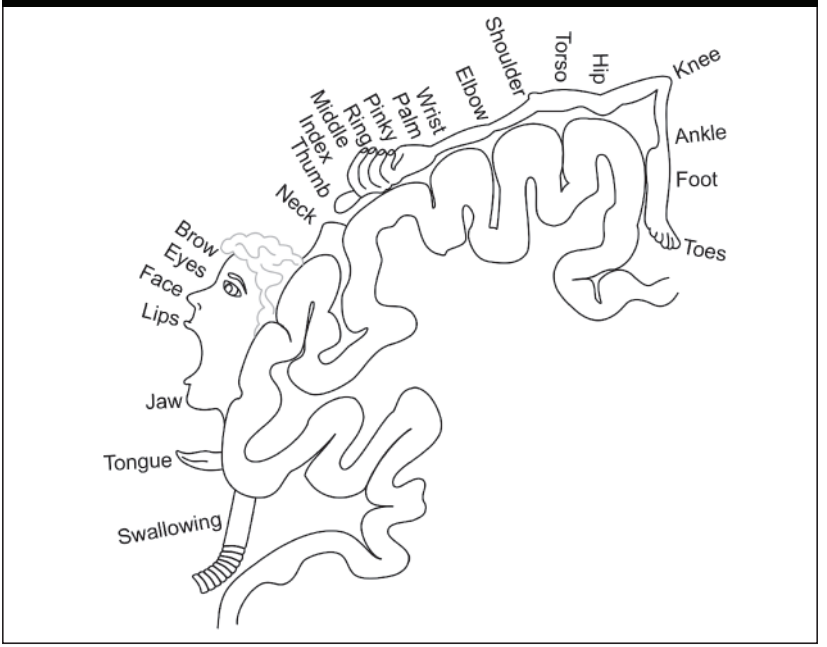
Information coming into our brains from our sensory systems provides us with knowledge about the external world, as well as about our own bodies, which the brain uses to create percepts that we experience as seeing, hearing, and feeling. These are called ascending systems because they project up to the brain from the eye or from the ear or from our body. In this lecture, our focus will primarily be on a descending system—brain areas and pathways that allow us to make a voluntary movement of some part of the body (below the neck).

The motor system is generally subdivided into a number of subsystems (pyramidal, extrapyramidal, and cerebellar); while this has some heuristic value, it is important to understand that all of these subsystems work together in normal movement. The *pyramidal motor system* is involved primarily in the initiation of a motor movement. It is called pyramidal because the neurons in Area 4 which give rise to this pathway are shaped like pyramids; it is also called the corticospinal pathway because the cell bodies of origin are in the motor cortex (Area 4) and their axons project to and synapse in the spinal cord.

Areas rostral to Area 4 in the frontal lobe receive widespread projections from higher-order sensory and multimodal areas of the cortex, and are involved in the planning of a motor movement; these neurons then project to Area 4. Motor cortex contains an orderly representation of the contralateral half of the body (Figure 17.1), with a disproportionate amount of cortex devoted to movement of the mouth and hands (fine movement necessary for speech and dexterity).

Axons of Area 4 neurons make up the corticospinal tract; the corticospinal tract will project down through the brainstem, decussate or cross in the lower medulla, and enter the spinal cord (see Figure 4.1). At the appropriate level of the spinal cord, axons will leave the pathway and enter the gray matter of the cord to synapse upon *anterior horn cells*; for example, motor neurons representing the leg on the medial aspect of Area 4 project to

Figure 17.1



A drawing showing the organization of the motor cortex in humans.

lumbar regions of the spinal cord. It is the anterior horn cells of the spinal cord that will project their axons *ipsilaterally* (on the same side) to the muscle to cause contraction.

Indirect corticospinal pathways also exist; in these pathways motor cortex projects to some nucleus or nuclei, generally in the brainstem, which then projects to the spinal cord (hence the name "indirect" corticospinal); these pathways are involved in other functions important to movement, for example, the maintenance of background "tone" in antigravity muscles. The *extrapyramidal motor system* is involved in the execution of subconscious motor programs (for example, the swinging of the arms during normal walking), and also some forms of learning.

It includes a number of deep nuclei of the hemispheres such as the *basal ganglia* nuclei (caudate, putamen, globus pallidus) and the subthalamic nucleus, as well as the *substantia nigra* ("black substance") of the midbrain. The nuclei of the extrapyramidal motor system do not project directly to the spinal cord; they are involved in feedback circuits which either project to nuclei which do project to the spinal cord (for example, some of the nuclei involved in the indirect corticospinal pathways), or importantly, back to the primary motor cortex to modify transmission in the corticospinal pathway.

So, how do the nuclei of the extrapyramidal motor system, as well as the cerebellum, know what the motor cortex wants to do? As the corticospinal pathway projects to the spinal cord, it sends off *axon collaterals* to many areas (see Figure 4.1), informing the basal ganglia and cerebellum about intended movement. This projection of axon collaterals off of major pathways is one of the ways that different areas of the brain are interconnected—it is truly a daunting task to determine all of the connections of even a single area of the brain!

Many different clinical disorders result from damage to structures of the extrapyramidal system. A *unilateral* lesion of the subthalamic nucleus, most commonly occurring from strokes, can bring about a terrible disease called hemiballismus, which causes flinging ballistic movements of the limbs. In a genetic disorder called Huntington's chorea, the caudate and putamen

lose a single type of neuron, causing individuals to experience abnormal, uncontrollable writhing movements of their bodies. ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. You want to scratch you right elbow with your left hand. What areas of the brain are involved in your ability to make even this simple movement?

2. Why does damage to the corticospinal tract cause paralysis, while damage, say, to the extrapyramidal motor system, does not?

The Motor System—Coordinated Movement

Lecture 18

We basically have three systems that are actually going to allow us to make a motor movement. We have our pyramidal system, which again is our "direct" and "indirect" corticospinal pathways. We have an extrapyramidal system, which is very, very complicated, and … we have the cerebellum, and the cerebellum is just an incredible structure.

Voluntary movement is planned by the cortex, and executed by the corticospinal tract. Indirect corticospinal and extrapyramidal pathways play a role in regulating movement as well. Coordination of movement, especially learned, skilled motor movement, however, is largely under the control of a fist-sized structure at the base of our brains referred to as the cerebellum. This "little *cerebrum*" allows for the proper timing and execution of movement, and for the correction of errors during ongoing movement. Therefore, we could not walk, play, or dance without a cerebellum.

Traditionally, the cerebellum has been considered a major structure of the motor system, coordinating motor movement; here we will discuss some of the motor functions of the cerebellum, and then end with a brief description of studies suggesting that the cerebellum plays a critical role in cognitive behavior as well. Amazingly enough, of the 100 billion neurons in the human brain, half are packed into the cerebellum!

The major motor functions of the cerebellum include a role in the maintenance of equilibrium and posture; the regulation and timing of motor movement, especially learned, skilled motor movement; and the correction of errors during ongoing movement.

The term cerebellum means "little cerebrum" because its organization is similar to the cerebrum in many ways. There are two hemispheres, an outer cortex or mantle of gray matter, and underlying white matter and nuclei. The cerebellar hemispheres are covered by a layer of cortex which can be divided into lobes by deep fissures. In humans, the surface area of the cerebellar

cortex is about 75% that of the cerebral cortex. Different areas of the cerebellum are also of different "ages" phylogenetically.

Courtesy of the National Library of Medicine.

Johannes Purkinje.

Cerebellar cortical organization is also different from the cerebral cortex in major ways:

- There are no Brodmann areas in cerebellar cortex.
- The cerebellar cortex is made up of three layers throughout: a surface or molecular layer, Purkinje cell layer (named after the anatomist and physiologist Johannes Purkinje), and a granule cell layer. The Purkinje cells are the only neurons to project out of the cerebellar cortex.
- Therefore, of the up to 50 to 70 billion neurons in the cerebellum, only the 15 million Purkinje cells project out of it, meaning that there's a huge amount of integration occurring in the cerebellum.

The cerebellum receives input from Area 4 via the pons, structures of the extrapyramidal motor system, and sensory input (for example, proprioceptive input from the spinal cord). Like the extrapyramidal system, the cerebellum has no direct projections to the spinal cord; it exerts its influence on motor behavior by feeding back to the other motor systems.

The cerebellum plays a critically important role in the coordination of learned, skilled movement. Essentially the firing patterns of cerebellar Purkinje neurons become synchronized as we learn fine motor skills; these neural circuits are reinforced with practice. From learning to walk to playing basketball, golf, piano, and dancing, any motor movement that improves with practice involves the cerebellum.

The cerebellum can be compromised by hereditary disorders, stroke, tumor, vitamin E deficiency, viral infection, trauma, and excessive use of alcohol. A number of changes occur from cerebellar damage:

- Dysmetria is an abnormal "timing" of movement.
- Dysdiadochokinesia indicates a "decomposition" of movement.
- Dysrhythmia means an abnormal "rhythm" to movement.
- Ataxia is a lack of coordination. When police require "tandem" walking (walking a straight line with one foot in front of the other) as a test for DUI, they are checking cerebellar function.
- *Intention tremor* is a tremor or involuntary movement that is primarily seen at the end of a movement, particularly when a fine motor movement is made.

Neuroscience has also discovered that the cerebellum plays a role in almost everything that goes on in the brain—from language to coordinating sensory input to the brain. As well, cerebellar abnormalities have been reported in a number of disorders, including autism and attention deficit disorder. ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. My students always laugh when I say that Michael Jordan has a beautiful cerebellum! Why do you think I say that? What about Tiger Woods?

2. Circuits that allow for the sequential and appropriately timed firing of muscle groups get established in the cerebellum with practice. Relate this to your own experience with learning how to dance, to play the piano, or to ride a bicycle.

Parkinson's Disease

Lecture 19

We would like to … provide a review of the motor system by comparing and contrasting the signs and symptoms you see in patients that have damaged different parts of the subsystems involved. We are going to try to focus a little bit more on *Parkinson's disease*, because it's the second most common neurological disease in the United States.

This disorder arises when a threshold number of neurons is lost from a single midbrain structure called the substantia nigra. This loss removes a major dopaminergic input to forebrain structures involved in regulating movement. We will then discuss strategies that have been or are currently used to treat this disorder. Here we will use clinical examples to reinforce information about the motor system. Our presentation is simplified, and it should be understood that each of these disorders is more complex than as presented.

The pyramidal or corticospinal pathway is involved primarily in the initiation of a motor movement. Injury to this system causes paralysis (an inability to initiate or produce movement) in some part of the body. Spastic paralysis can result if indirect corticospinal tracts are also involved. Patients with spastic paralysis exhibit increased reflexes and abnormal muscle tone. If neurons traveling from Area 4 have been damaged before they cross over to enter the spinal cord, signs and symptoms are contralateral. If they are damaged after they cross, signs and symptoms are ipsilateral.

Damage to anterior horn cells in the spinal cord will also produce paralysis; here damage on the right will produce a paralysis on the right (remember that axons coming from Area 4 cross or decussate in the medulla to enter the spinal cord on the contralateral or opposite side); here the paralysis is referred to as flaccid paralysis because the paralyzed part of the body will show a decreased tone and decreased reflexes.

An individual who severs the spinal cord at cervical (neck) levels (like the actor Christopher Reeve) will be completely paralyzed from the neck down

(a disorder called *quadriplegia*). Any movement which remains is most likely due to some intact axons that were not damaged; such an individual is unable to receive sensory input from the body as well, since all ascending axons have also been severed. Quadriplegics are believed to undergo subtle emotional changes because they no longer receive information coming from the body.

Another disorder affecting the motor system is *amyotrophic lateral sclerosis* (ALS), also known as Lou Gehrig's or motor neuron disease. ALS causes loss of motor neurons in the cortex and spinal cord at different rates and at different times, until the individual becomes completely paralyzed. The term ALS is derived from the findings at autopsy of a muscle loss (due to the loss of innervation of muscle by motor neurons in the spinal cord) and of a hardening of the lateral areas of the spinal cord (due to replacement of degenerating corticospinal axons by astrocytic scars).

A lot of men who were in Europe [during World War II] came back with encephalitis. One of the diseases that they demonstrated later in life was advanced Parkinsonian signs and symptoms, and this is because the flu got into their brain.

The cerebellum plays a critical role in the coordination of motor movement, especially fine, skilled movement. Thus an individual with damage to the cerebellum is not paralyzed and can initiate a motor movement but has difficulty with motor coordination. The nuclei and areas of the extrapyramidal motor system are complexly interconnected and there is a delicate balance of excitation and inhibition between these nuclear groups. Damage to individual nuclei generally alters this balance, resulting in abnormalities of movement; Parkinson's disease will be used as an example.

Parkinson's disease, named after James Parkinson, is the second most common neurological disorder in the United States. When an individual loses substantia nigra neurons in the midbrain due to a known insult or injury (for example, carbon monoxide poisoning), the term Parkinsonian is used to describe the resulting signs and symptoms; if there is no known cause for

the loss (in medicine this is referred to as *idiopathic*), it is called Parkinson's disease (here we will use the latter term).

In projections of the substantia nigra to other extrapyramidal motor structures, dopamine acts as both an excitatory and an inhibitory transmitter; in normal individuals, the inhibitory pathway acts as a "brake" on the excitatory pathway. In Parkinson's disease the loss of substantia nigra neurons causes (ultimately) the excitatory pathway to be underactive and the inhibitory pathway to be overactive. Initially in the disorder, the individual develops a *resting tremor* (a shaking that occurs at rest or when there is no movement being initiated), short shuffling steps, a stooped posture, and other abnormalities. The individual will also show a lack of normal automatic movements, for example, the swinging of the arms during walking. As the disease progresses, movement is inhibited; the individual "freezes" and is unable to make a normal movement. Individuals show little facial expression, but are cognitively aware.

A variety of strategies, each with their own problems and complications, have been used to treat this disorder. Pharmacological intervention involves trying to replace dopamine; unfortunately the dopamine receptors become hypersensitive to the drugs, resulting in abnormal movements which can be debilitating themselves. Transplants of embryonic dopaminergic neurons or homografts from other areas of the body that produce the catecholamines have been made with limited success, but over time many or all of the cells die. Lastly, electrodes can be implanted in the brain. These electrodes stimulate another nucleus in this complicated circuit, effectively "lesioning" one of the nuclei that is overactive in the disease. Of course, both transplantation of cells and implantation of electrodes require brain surgery, which involves serious risk. Nonetheless, in individuals with brain stimulators, it is literally miraculous to see the changes in their ability to move. ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. Unfortunately, Parkinson's disease is often viewed as a relatively benign disorder. But imagine the options for the individual: Be frozen, take medications that may produce side-effects that may be worse than the disease, or risk brain surgery! What were your ideas about this disorder before this lecture?

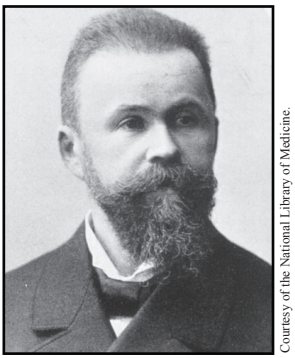
2. Pesticides and herbicides have been implicated in Parkinson's disease. Some scientists believe that our exposure to such agents over a lifetime is responsible for the high number of cases seen in older individuals. What other causes for Parkinson's have been proposed and studied in recent years?

Language

Lecture 20

Language involves higher-order sensory areas and higher-order motor areas. That should make sense to you. For example, auditory areas are involved in the ability to interpret spoken language as meaningful, so this is going to be the function of a higher-order sensory area. Motor areas are going to be involved in the ability to produce the specific combinations of sound that compose a given language and which are meaningful to any native speaker.

While other animals may communicate in subtle and complex ways, the ability to communicate symbolically through language is believed to be unique to humans. Our earliest hominid ancestors show skeletal specializations indicating that language arose at the dawn of our evolution. In parallel, however, areas of the brain dedicated to speaking and understanding language had to be selected for as well. Asymmetries between the hemispheres in brain areas involved in language are apparent even during fetal development in humans. And while every neurologically normal individual learns to speak language, not every human being will be literate. We will review the evidence that certain areas of the brain play a role in both spoken and written language.



Courtesy of the National Library of Medicine.

Karl Wernicke.

Our species appears to be unique in our ability to communicate symbolically through language. In fact, language appears to be instinctual in our species. Skeletal specializations have been identified in our earliest hominid ancestors that would allow for speech. While an individual language is learned, the ability to recognize the individual *phonemes* of any language is present in humans at birth; areas of the left hemisphere specifically involved in language show asymmetries even before birth.

A language is composed of a number of elements. There are approximately 6,000 separate, and equally complex, languages spoken on earth; each uses a subset of sounds which can be produced by the vocal cords; for example, there are around 50 specific phonemic sounds in English (for example, /b/ and /c/). *Morphemes* are the simplest arrangement of phonemes into a meaningful grouping (for example, syllables). Simple words in a language are different and distinguished from each other by phonemes and morphemes.

Words in turn make up sentences or temporal strings of words that have meaning. This meaning is largely accomplished by grammar and syntax. All languages show a "word order" in which there is a subject, a verb, and an object; meaning is, in part, conveyed by this word order; different languages have different word orders.

Language areas, primarily of the left cerebral cortex (the left hemisphere is generally dominant for language even in left-handed individuals), map the form of any language to "meaning". In the 19th century, Paul Broca (1824–80) and Karl Wernicke (1848–1905) described patients with specific acquired language disorders called *aphasias*; the two major areas of the brain associated with language bear their names.

- Broca's area (left inferior frontal gyrus; Areas 44 and 45) is involved in the motor production of language; an individual with *Broca's aphasia* can no longer speak language normally, but can understand what is said.

- Wernicke's area (left superior temporal gyrus; Area 22) is an area associated with the ability to understand spoken language; an individual with *Wernicke's aphasia* can no longer understand language, but can speak fluently (although what is said is generally meaningless).

Broca and Wernicke's areas are connected, and a different type of aphasia can result from damage to these connections. Even though the left hemisphere is usually dominant for both the production and interpretation of spoken language, the right or nondominant hemisphere does play a role in

normal language; for example, *prosody* (the so-called "musical" properties of a given language) is a function of the right or nondominant hemisphere. Lesions in the nondominant hemisphere in the area comparable to Broca's area cause individuals to speak in flat tones; individuals with lesions of the area comparable to Wernicke's area in the nondominant hemisphere cannot understand the emotive element present in the prosody of others' language. The same areas involved in language development in individuals who use spoken language are also involved in sign language; damage to the left or dominant hemisphere in signers produces comparable aphasias.

So language, this incredibly unique capability that we alone as humans have, helps us communicate with others, organize our sensory experience.

In contrast to what may be an instinct for spoken language, written language is an invention, and must be acquired through instruction. In other words, every neurologically normal person learns how to speak language, but not every person will be literate. Even though reading and writing must be taught, the left hemisphere is designed to abstract the rules of written language. Thus, there are areas in the human brain that underlie the ability to read and to write. Damage to Areas 39 and 40 in the left (or dominant) parietal lobe causes an "acquired illiteracy" in an individual who could formerly read and write; what is lost is not the ability to see words, but rather the ability to map what is seen to meaning.

In humans, language is not just about communication. Language helps organize sensory experience. Most obviously, we categorize objects in our world largely by language constructs that are actually fairly difficult to define, but once a word's meaning is mapped in your brain, you cannot lose that ability unless there is damage to the brain. Individuals can lose particular parts of speech such as nouns. Note also that thought, at least in part, also has a lot to do with words, consisting of an internal manipulation of words.

The role of the brain in spoken or written language is very complex. Some aspects of language become habitual and are probably controlled by the extrapyramidal motor system. This is confirmed by the fact that individuals

with disorders of the latter system may show subtle language impairment as well as motor dysfunction. Other brain areas are implicated as well, particularly in bilinguals. Individuals who acquire more than one language as children appear able to think in each language without translating. We also find that after puberty, Broca's and Wernicke's areas appear to lose some plasticity, making it difficult to learn foreign languages after this time.

Language is among the most higher-order of the cognitive functions associated with our species, and it plays a fundamental role in our engagement in the world, especially with other human beings; spoken language not only communicates facts and helps organize sensory experience, but allows us to attempt to communicate our innermost feelings and thoughts to others. ■

Suggested Reading

N. Chomsky, *New Horizons in the Study of Language and Mind.*

S. Pinker, *The Language Instinct.*

L. Vygotsky, *Thought and Language.*

Questions to Consider

1. It has been shown recently that great apes and some monkeys, which show left hemisphere asymmetries similar to humans, also have a "Broca's" area. "Mirror" neurons have been identified that are associated with acquisition of actions and sounds that are learned and that play a role in "gesturing" and "vocalizations" essential for social communication in nonhuman primates. In what ways do humans use language for *social* communication?

2. In what ways do we communicate *nonlinguistically*?

The Limbic System—Anatomy

Lecture 21

Now, in this and the next few lectures, we are going to be talking about a very, very different system. This system is called the limbic system—we are going to be discussing why it's called that. It's with the limbic system that we are engaged with the world.

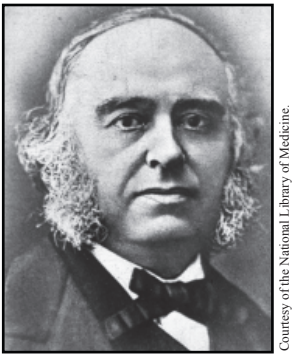
Our sensory systems allow us to know about our external world and receive information about it while our motor system allows us to act in the world. Intercalated between inputs and output are major integrative systems that play an active role in deciding what, and how, information coming into the brain will be processed. One of the most intensely studied of these integrative systems is the limbic system. Early neuroanatomists noted that structures located at the "limbus" or "edge" of the brain hemispheres played critical roles in emotion and memory. The number of structures included in this system has expanded as has its definition in modern neuroscience. As currently conceived, the limbic system represents a large number of complexly interconnected nuclei and areas which together allow for learning, memory, emotion, and executive function.

The limbic system of the brain allows for learning, memory, and emotion, all of which influence executive function. Here we will briefly mention some of the anatomical structures composing this large and complexly interrelated system. As we talk about the limbic system, consider how it provides us with the emotional texture that allows us to engage with the world.

To understand the modern conception of the limbic system, we need to appreciate the evolution of the idea of a system devoted to these interrelated functions. In 1878, the French neurologist Paul Broca (1824–80) identified "*le grand lobe limbique*," referring to a ring of gray matter on the medial aspect of the hemispheres (hence the name "limbic" or border/edge) that were thought to play a critical role primarily in emotion. In the 1930s, the comparative neurologist James Papez (1883–1958) defined a limbic system by identifying particular pathways and structures that might underlie the

association between memory and emotion; one of these pathways is known as the Papez circuit.

The Papez circuit is composed of the hippocampus (memory), mammillary bodies (specific nuclei in the hypothalamus), anterior nuclei of the thalamus, and the cingulate gyrus (a ring of gray matter just above the corpus callosum). All of these nuclei are interconnected into a feedback circuit or loop allowing for the integration of emotion and memory.



Courtesy of the National Library of Medicine.

Paul Broca.

From the late 1950s, additional nuclei and cortical areas were identified as part of a limbic system and over the years, the system, and our understanding of how all of these elements are important in learning, memory, emotion, and executive function has grown.

A few of the nuclei in the limbic system discussed in this lecture include the following areas:

- The hippocampus (seahorse) and entorhinal cortex are both temporal lobe structures involved in learning and memory.

- The *amygdala* (almond-shaped), a small *subcortical* nucleus located under the cortex at the temporal pole of the brain, is known to be involved in the processing of emotions, especially fear, and it also plays a role in emotional memory.

- The *ventral tegmental area* (VTA), a small group of dopamine-containing neurons in the midbrain, plays a role in an *endogenous reward system*.

- The *nucleus accumbens septi* is a forebrain nucleus which receives a major input from the VTA.

- The hypothalamus, the area of the diencephalon composed of many nuclei regulating autonomic, endocrine, and visceral functions, is also part of the limbic system. For example, the hypothalamus regulates *sympathetic* (fight or flight) and *parasympathetic* (rest and relax) divisions of the autonomic nervous system.

- The *orbitofrontal cortex* (above the orbit of the eye) is involved in impulse control, inculcation of cultural mores, and the ability to appreciate the consequences of one's own behavior.

- The *dorsolateral prefrontal cortex* appears to have more of an involvement in executive function in humans, contributing to our ability to prioritize behavior and to adapt to change; because executive function is influenced by emotion, it is included here.

Early awareness of the role some of these areas play in human behavior arose because of two very famous clinical cases:

- Phineas Gage was a dynamite worker who in 1848 survived an explosion that blasted an iron bar (3'7" long, 1.25' wide) through the front of his head; he showed profound (negative) changes in his personality. The damage was primarily localized to the orbitofrontal cortex, which plays a critical role in the abstraction of rules, social conduct, and mores.

- H.M. was a patient who underwent a bilateral temporal lobectomy for epilepsy in the early 1950s. Following surgery he developed global amnesia; although he did regain some long-term memory and some motor skills, after surgery he was unable to learn new information; damage was primarily to medially located temporal lobe structures (hippocampus). ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. Surely one of the most important—and intriguing—findings in modern neuroscience has been that prefrontal cortical areas involved in higher-order cognitive behavior and personality undergo reorganization under the influence of hormones at puberty. Do you feel more of a kinship—cognitively and emotionally—with *who you were* as a child, or *who you have been* since your early 20s? Why?

2. Given what you have learned in this lecture, can you explain why some adults who were brutalized either by physical or psychological abuse as children show abnormalities specifically within limbic system structures?

The Limbic System—Biochemistry

Lecture 22

What is our definition of the limbic system in the modern neuroscience era? It's this huge, mega, integrated system of complexly interconnected nuclei that play a role in learning, memory, emotion, and executive function. Now you are beginning to see why I place executive function in that limbic system.

In the previous lecture, we reviewed how the concept of a limbic system consisting of nuclei and areas in the CNS critically involved in learning, memory, emotion, and executive function arose. These areas are connected via complex circuits, utilizing a variety of neurotransmitters or neuromodulators. In this lecture, we will discuss some of these neurotransmitters/neuromodulators that are especially important in the normal functioning of the limbic system circuits, either because they are utilized by limbic system structures or by neurons which project to limbic system structures.

Major emotional disturbance, personality changes, and cognitive dysfunction can occur from either lesions or other damage to nuclei, or to disruption of the neurotransmitter balance in this system. Like the extrapyramidal motor system, the limbic system has complex feedback circuits. But if an individual suffers damage to one of the nuclei of the limbic system, instead of displaying changes in motor skills, that person displays profound changes in the way he or she relates to the world.

The limbic system is complexly interconnected with another integrative brain system called the reticular formation. Nuclei of the latter system play critical roles in sleep, arousal, attention, and maintenance of consciousness. To appreciate the interconnection of these two systems, just think how your mood (limbic system) changes when you don't get enough sleep (reticular formation)!

Projections to limbic system structures (primarily from reticular formation) and the projections between limbic system structures involve various neurotransmitters:

- Glutamate is the major excitatory neurotransmitter in the CNS and is used by many of these projections.

- Serotonin (5-HT) is a monoamine used primarily by *raphe* (midline) *nuclei* in the reticular formation. Raphe nuclei are a collection of cellular groups extending from the medulla up into the midbrain.

- Dopamine is a neurotransmitter used by the VTA located in the midbrain. It is a major player in addictions.

- Norepinephrine is a neurotransmitter used primarily by the *nucleus locus coeruleus*, a small but important nucleus of the pontine region of the reticular formation involved in a variety of functions including selective attention, the regulation of blood flow in the brain, and sleep/wake cycles.

- GABA is a major inhibitory neurotransmitter in limbic system projections and is also used by many interneurons in limbic structures.

You can … lead people to think that an outcome of something will be positive or negative, and they will report having an internal positive or negative sensation even though the body sensation is exactly the same.

Other neuromodulators, including hormones, are involved in this system:

- *Opioids* are naturally occurring "morphine-like" peptides in the brain (for example, endorphins); they are found in areas of the brain involved in physical and emotional pain modulation.

- Hormones, like *oxytocin* (the "love" molecule), a peptide hormone released by the hypothalamus, plays a role in a number of processes, including bonding in social animals.

The limbic system also gives us what we refer to as *mood* and *temperament*, which neuroscientists define separately.

- Mood is an emotional response that fluctuates.

- Temperament is a stable characteristic of individuals related to how their limbic system is wired.

Neuroscientists have also made a distinction between an *emotion* and a *feeling*.

- An emotion is a basic physiological state that has to do with your autonomic nervous system and the changes that take place in your body as a result of the limbic system's reaction to something.

- A feeling is the internal subjective state that you experience.

We have learned that feedback from the body is important in the brain's construction of "feeling." The brain uses the feedback from the body, in part, to construct an appropriate feeling. This recognition has been important for understanding the emotional blunting that can occur, for example, in patients following the complete transection of the spinal cord at cervical (neck) levels. The limbic system takes our experience, our expectations, the social context of our lives, and other factors and constructs the appropriate feeling, whether it is positive or negative. ■

Suggested Reading

C. Pert, *Molecules of Emotion.*

Questions to Consider

1. Many of the body reactions are similar when we are angry and when we are ecstatic. Given what you have learned in this lecture, why are our "feelings" different in the two cases?

2. Is there any reason to think that just because a strong emotional attachment like "love" has biological and biochemical correlates in the brain—that it is any less important in human existence?

Depression

Lecture 23

Depression is, in fact, very common. It can be very, very broadly categorized into two main groups. Depression is a very complex disorder, but we are trying to simplify it here. So there are two very broad categories. One would be reactive depression, which is a normal response of the brain to loss. … In addition, human beings are somewhat unusual in that we also have strong bonds with ideas and things. Sometimes the loss of trust, for example, can devastate people.

Depression would appear to be the scourge of modern societies, with literally millions of prescriptions written for antidepressant drugs. Here we will focus primarily on unipolar depression, a CNS disorder which has known anatomical and biochemical correlates. We will also discuss how the three major classes of antidepressants work, and what led to the development of the so-called "designer" drugs for depression.

Depression is a relatively common disorder categorized as either reactive or clinical (unipolar) depression. Reactive depression is a normal response of the brain to loss, for example, from the death of a loved one, or loss of trust. Clinical or unipolar depression is believed to be a medical condition resulting from the imbalance of neurotransmitters within the limbic system. Clinical or unipolar depression is characterized by profound despair and hopelessness. *Manic depression* or *bipolar disorder* consists of cycles of debilitating depression alternating with periods of exhilaration.

Here we will keep our discussion general in terms of what structures and neurotransmitters are believed to be primarily involved in depression, with the understanding that any type of depression probably involves many of the same circuits and neurotransmitters. The major neurotransmitters implicated in depression are the monoamines (or biogenic amines), including the catecholamines, dopamine and norepinephrine, and the indolamine serotonin or 5-HT. In general, increasing levels of monoamines promote a feeling of well-being.

The so-called "antidepressant" drugs primarily alter the levels of monoamines. Specifically, these drugs facilitate synaptic transmission in monoaminergic pathways. The fact that such drugs act as antidepressants led to an early hypothesis (the *biogenic amine theory*) that depression results from a functional deficiency of these neurotransmitters in the limbic system. Antidepressants are generally classified into three categories.

- Tricyclic antidepressants inhibit the reuptake of all of the monoamines; preventing reuptake increases the amount of neurotransmitter available at the synapse. Tricyclics can cause some individuals to become more depressed (called a paradoxical effect), and in some individuals, tricyclics can increase the likelihood of suicide. Tricyclics are generally not effective with reactive depression.

- Monoamine oxidase (MAO) inhibitors increase *endogenous* levels of the monoamines by preventing their breakdown by the enzyme MAO. AO inhibitors also alter the metabolism of *a dietary* amino acid (tyramine). If an individual eats food high in tyramine *(for examp*le, cheese) while taking MAO inhibitors, a hypertensive crisis and possibly hemorrhagic stroke (bleeding in the brain) may occur; for this reason, lists of proscribed foods are given to individuals taking MAO inhibitors.

- Designer antidepressants were created because of the potential unwanted effects of tricyclic and MAO inhibitor antidepressant drugs, and because the latter drugs were not very specific in their action. The first designer antidepressant drug Prozac (fluoxitine hydrochloride) was released in 1987; it works primarily by blocking the reuptake of serotonin; drugs of this class are called selective serotonin reuptake inhibitors (SSRIs).

The response of individuals on Prozac ranges from no effect at all to "transformational." Severe anxiety and decreased libido can be side-effects of Prozac in some individuals.

Prozac has been used to treat reactive depression, *obsessive-compulsive disorder* (OCD), panic, anxiety, eating, and other substance abuse disorders; there is some reported success with controlling violent behavior; Prozac is also marketed under the name Sarafem for the treatment of premenstrual dysphoric disorder.

A great deal of research is oriented towards understanding depression because it's very common in our society.

Many other prescribed antidepressant drugs are available, some SSRIs, some not. The fact that these drugs are used to treat a wide variety of disorders and that they have different effects in different people suggests that many different pathways in the limbic system can be involved in any given individual.

Research is needed to better understand depression. Recent findings include that depressed individuals who commit suicide have structural lesions in their limbic system not found in nonsuicidal, depressed patients. Clearly, depression is a very complex disorder. ■

Suggested Reading

K. Jamison, *An Unquiet Mind.*

P. D. Kramer, *Against Depression*.

W. Styron, *Darkness Visible.*

Questions to Consider

1. Given the overwhelming data in support of depression being a "disorder" of the brain, why do you think that, in general, our society treats depression as though it were a character flaw and not an illness?

2. Of what *value* is emotional pain? What might be a number of negative consequences to prescribing antidepressants for "reactive" depression?

The Reward System—Anatomy

Lecture 24

In this lecture, I want to talk with you about a subsystem of this mega-limbic system. This subsystem is the system that's responsible for creating that internal positive or euphoric feeling we have when we engage in pleasurable activities. So whether that's reading a book, whether it's viewing a sunrise, whatever it is, maybe taking a course, doing something that we enjoy, this is the system that is tapped into.

As humans, we have an enormous range of emotional responses to life events. In addition to the depths of depression, we are also capable of experiencing a true joie de vivre. All animals, in fact, seek out and engage in behaviors that are rewarding or which bring them pleasure. Here we outline briefly the brain structures and neurotransmitters that have been identified as part of an endogenous biological reward system. This system is believed to be responsible for the internal positive and even euphoric feeling we experience when engaging in activities as diverse as interacting with friends, reading a good book, or viewing a sunset.

We know from observation that normally individuals seek out activities which bring them pleasure or are rewarding, and thus contribute to a sense of well-being. These and other observations suggested that an underlying system existed in the brain that was responsible for the subjective experience of pleasure that occurs when we interact with friends, do a job well, or appreciate the beauty of a sunset; this system was conceptualized as an endogenous reward system. We have previously seen how, in general, increasing the level of the monoamines increases feelings of well-being, and can, at least in some individuals suffering from depression, have an antidepressant effect.

The endogenous reward system is both a neuroanatomically and neurobiochemically defined system involving a subset of nuclei and pathways of the limbic system, and projections to limbic system structures (primarily from reticular formation nuclei). Anatomically, a number of specific areas are involved, including the following.

- The VTA of the midbrain (mesencephalon) gives rise to "meso-limbic" (primarily to nucleus accumbens septi) and "meso-cortical" projections (primarily to prefrontal cortex). It utilizes dopamine as a neurotransmitter.

- The nucleus accumbens septi (or nucleus accumbens), a major forebrain nucleus of the limbic system, receives its major input from the VTA. It plays a role in addictive behaviors.

- Areas of the prefrontal cortex, in particular, the orbitofrontal cortex, are also involved in this system.

Biochemically, dopamine is the major neurotransmitter, although other neurotransmitters or neuromodulators, and even hormones, are also involved; for example, opioids and oxytocin play a role in reward.

What experimental and clinical data support the conclusions that an endogenous reward system exists? Experiments in animals identified areas of the brain that seemed to induce a pleasurable state; if an animal was trained to press a lever to receive brain stimulation in these areas, they would choose to bar press over food, water, or sex. Such animals will self-stimulate till exhaustion!

And so we need equally to care about depression, but also about exuberance.

Other studies demonstrated that positively rewarding behaviors, either natural (e.g., involving feeding, drinking, sex) or unnatural (e.g., brain stimulation), could be abolished by lesioning or damaging these areas of the brain. Experimental studies in animals, and now studies in humans confirm, that addiction to drugs like cocaine stimulates many of these same brain areas, and is likely to play a role in producing the artificial "high" or elation. These same areas of the brain also appear to be activated when we anticipate pleasure! Lastly, but importantly, damage to areas of this endogenous reward system can abolish a person's ability to experience the joy or exuberance of life!

If dopamine is the major neurotransmitter for this system, why don't we help people who are depressed by giving them drugs to increase their levels of dopamine? Increasing levels of dopamine produces mania, an artificial elation, and individuals can become addicted to those highs; increasing levels can also cause psychosis. Individuals who experience manic depression may be noncompliant with their medications because they do not want to "level out" emotionally. ■

Suggested Reading

K. Jamison, *Exuberance.*

W. Styron, *Darkness Visible.*

Questions to Consider

1. Chocolate and exercise are two things that have been found to stimulate the endogenous reward system. What various activities do you engage in to stimulate your reward system?

2. Even *thoughts* about friends and loved ones can increase activity in the reward centers of the brain. Can you think of reasons why such a system—responding to reward or anticipation of reward—might have been selected for in evolution?

The Reward System—Drugs

Lecture 25

I would like to highlight our current understanding about how this endogenous reward system can actually be hijacked when you take a drug from the external world—which we say is exogenous—when you take a drug like cocaine into your body.

We will also review data suggesting that these same areas of the brain play a role in addictions to other drugs, and in behavioral "addictions" (e.g., eating, gambling) as well. Psychoactive drugs that produce euphoria, or a "high," do so by altering the biochemistry of the endogenous reward system. Such drugs can be both physiologically and/or psychologically addicting. There appears to be a gene-environment interaction implicated in drug dependence, with some studies indicating an increased heritability for drug dependence in females. Here, we will use two examples (cocaine and marijuana) to illustrate how many of these drugs are thought to affect the endogenous reward system of the brain.

Cocaine is an especially potent psychostimulant that is highly addictive; by blocking the transporter that takes dopamine back up into neurons after release, cocaine increases the amount of this neurotransmitter available at synapses, primarily in the nucleus accumbens; cocaine also blocks the reuptake of serotonin via the same mechanism Prozac blocks reuptake. When the neurotransmitter balance in these structures is disrupted by cocaine, there is an initial feeling of intense elation followed by a massive and rapid compensatory adaptation in these structures. The euphoric effects are followed by intense *dysphoria* or crash (depression, lethargy, and irritability) that can last for hours or days, and craving that euphoria promotes a rapidly escalating pattern of compulsive use. Tolerance also occurs with repeated use so that ever increasing doses are necessary for the same effect.

The long-term use of cocaine can produce permanent changes in the brain. Recent studies suggest there may be permanent changes in the responsiveness of neurons, particularly to dopamine, in the endogenous reward system in long-term users. In some long-term users, there may also

be a permanent down-regulation in the synthesis of naturally occurring opioids such as endorphins. The latter finding, in conjunction with the altered responsiveness to dopamine, helps explain why some long-term users show a permanently blunted emotional affect even when they are not using; this also contributes to the high rate of recidivism seen in cocaine addicts. Cocaine also adversely affects the dopaminergic projection from the VTA to the orbitofrontal area, which is involved in impulse control and the inculcation of cultural mores.

In moderate doses, marijuana has effects similar to alcohol; at higher doses it causes euphoria and heightened sensation. Contrary to popular belief, ⅔ of users show drug dependence, with anxiety, anger, and irritability upon withdrawal; drug dependence to marijuana can also be induced in animals.

Why the endogenous reward system and its definition was one of the greatest discoveries in the last 25 years is that we have also learned that this prefrontal area of the brain undergoes reorganization at puberty under the influence of hormones.

A number of areas in the limbic system have receptors which bind marijuana, or are affected by its use. These areas include the prefrontal cortex, VTA, hippocampus, nucleus accumbens, and amygdala. Effects on the prefrontal cortex may affect judgment and the ability to associate behavior with consequences, resulting in disinhibition and risky behaviors. It is implicated in a clinical disorder called *amotivational syndrome*, which is seen in chronic and long-term users of marijuana. The hippocampus also shows a high concentration of receptors that bind marijuana; significant impairment in memory is seen in some long-term users.

We have focused on cocaine and marijuana, but many drugs have similar effects. Most addicting drugs, for example, increase dopamine in the nucleus accumbens, although the underlying mechanisms may be different. The binding of drugs to brain receptors occurs not because the brain has cannabis

or cocaine receptors but because the brain has structurally similar *natural ligands* that bind to those receptors. One area of controversy is whether behaviors such as gambling and compulsive sex qualify as addictions; fMRI and *positron emission tomography* (PET) scanning do indicate that the same areas of the brain are stimulated. It is unknown, however, to what degree dopamine levels are altered in these behavioral addictions. Nonetheless, the "highs," compulsive nature, and willingness to risk everything to get a "fix" indicates that some behaviors can be addicting.

We clearly have much to learn about why some individuals become addicted to drugs, gambling, television, or pornography, and others do not. We also need to learn more about how the exposure to drugs in utero influences the development of the endogenous reward system, as well as how this system may be altered with drug use during adolescence and adulthood. ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. When an exogenous drug affects the brain, it means there are endogenous or normally occurring substances within the brain that bind at those receptors. Why do you think we have natural substances within the brain similar to morphine- and marijuana-like compounds?

2. Can you think of a number of neurobiological reasons why adolescent drug use could be particularly dangerous?

Brain Plasticity

Lecture 26

What have neuroscientists learned about what is going on in the brain when we learn something or we remember something? Well, if it's the connections that are involved, then it means that the changes have to occur at synapses. We call these changes *synaptic plasticity*, which implies that the synapse is not a static structure, it's a dynamic structure.

Far from being static structures, synapses are highly dynamic. This allows synapses to be modified by experience. This modifiability, which is referred to as *synaptic plasticity*, underlies learning and memory. Here we will look at a few of the ways synapses can be modified. We will mention briefly some of the areas of the brain that play a critical role in memory, as well as the neurobiological basis of why "memories" change with time. In normal development, migration of neurons and development of specific long-axon pathways that underlie various functions appear to be fairly hard-wired. Hard-wiring ensures that structures are correctly connected to one another.

It is clear that much of our behavior and response to the world is learned, however, and is thus dependent on experience. *Soft-wiring* refers to the brain's ability to enact change determined by our experience in the world. Areas of the limbic system, for example, which are easily modified, are more soft-wired. The questions are, "What does experience modify? In what ways are our brains soft-wired?" The answer to the latter question, and to the question of what has contributed enormously to our adaptability as a species, lies in our understanding of what learning and memory are about. Here we will look at what is known about these incredible processes.

Memory can be divided into a number of interrelated categories based on different functional and temporal features. Functionally, memory can be grossly divided into at least two broad categories. Explicit (declarative) memory includes memory of facts and words (semantic memory), and memory for events (episodic memory). Implicit (nondeclarative) memory consists largely of nonverbal memories, for example, motor habits.

- Temporally, memory is commonly divided into three categories, although it can be difficult to define precisely the temporal parameters:

Working or immediate memory, which is held for a very short period of time (less than 30 seconds).

Short-term memory, which is necessary for learning to take place.

- Long-term memory; although such memories may last a lifetime, they are modified by ongoing experience.

In terms of brain structures, a number of areas are involved in memory. Working memory appears to require participation of parts of the prefrontal cortex; individuals with damage to parts of the prefrontal areas have difficulty planning for future actions.

Short-term memory and the formation of new memories involves the hippocampus. The left hippocampus is more involved with memories involving language, and the right hippocampus with spatial memory. The left hippocampus is also believed to be a major player in the ongoing formulation of an "autobiography" or internally generated story constructed by the brain which is really a loose stringing together of episodic events—and which we experience as the story of our lives.

Implicit (nondeclarative) memory, which is more about "how to do something," is controlled primarily by structures of the extrapyramidal motor system and cerebellum. Emotional memory involves the amygdala (and probably some cortical areas as well). Long-term memory appears to be more widely distributed in neocortical areas, especially in "association" areas, which is why short of massive brain damage we do not lose long-term memory. Long-term memory is likely to involve changes in neurons, for example, in the expression of particular proteins.

Memory and learning involve changes—either physiological or structural—in synapses, and for long-term memory, in neurons. The ability of synapses to

be altered is referred to synaptic plasticity; changes at the synaptic level can take many forms, but the underlying mechanisms appear to be remarkably similar from sea slugs to humans. Increasing the amount of neurotransmitters released at a synapse augments the size of the postsynaptic potential, making the synapse more efficacious, and thus increasing the influence that synapse has on the firing of a postsynaptic cell. Spines, those little protuberances of the dendritic surface, can change shape under the influence of experience, and different spine shapes can also influence the efficaciousness of a synapse.

New synapses are formed throughout life, it turns out; and this is something modern neuroscience has uncovered.

Forming new synapses increases the influence of specific inputs to postsynaptic neurons; new synapse formation occurs throughout life in most brain areas. Long-axon neurons and interneurons can form new synapses. New synapses can be made (by remaining normal axons) after injury to the brain to replace injured axons. A learning experience can also induce new synapse formation.

Changes in brain organization as the result of learning can actually be observed with newer imaging methods; it is known, for example, that somatotopic maps are altered with experience; the area of the map involved in feedback from individual fingers, for example, is increased in the primary somatosensory cortex of individuals who play the violin and the piano!

Experiments have shown that blind animals can develop auditory or somatosensory areas in structures that would normally be involved in vision. It is thought the same thing happens in humans who are blind. ■

Suggested Reading

E. Kandel, *In Search of Memory.*

A. Margalit, *The Ethics of Memory.*

D. L. Schacter, *Memory Distortion.*

Questions to Consider

1. Early in the disease, individuals with Alzheimer's disease have the most difficulty with short-term and spatial memory. From this lecture, what have you learned about what area is most likely involved?

2. Accounts of Holocaust survivors are currently being recorded and collected for posterity. No other species considers that there is an "ethics" involved in such remembering. How do you think the collective memory of such horrific events from the past might help or guide us in the future?

3. In terms of everyday mundane behavior, how do past learning and memory *change* decisions made in the present? How could we make decisions if we had no learning or memory to consult?

Emotion and Executive Function

Lecture 27

What we want to discuss in this lecture is a new paradigm. That new paradigm says that emotion plays a role in this [decision-making] process, that it's emotion which guides us in being able to choose between various options.

The dichotomy of rational thinking and emotional behavior is part of Western intellectual history. Modern neuroscience, and particularly data collected on patients with specific types of brain damage, however, suggest that truly rational behavior is not possible without emotion. The importance of emotion in cognition and behavior is reflected in the tremendous elaboration in humans of the structures that comprise the emotional brain, as well as other areas of the limbic system which are considered "executive" in function. The numerous interconnections between these and other structures suggest that emotion, memory, and cognition all participate to increase adaptive behavior, in part, by allowing meaning to be given to our experiences which can then be used to influence and guide future behavior.

Philosophers, psychologists, and neuroscientists have all pondered the role of emotion in human behavior. The Western philosophical tradition has historically ascribed to some type of Dualism; Descartes is most notable (rightly or wrongly) for separating mind and body; an extreme Dualism sees emotional behavior as antithetical to rational behavior. Here we will look briefly at a different view: that emotions, and in humans the mental representation of emotions that we subjectively experience as "feelings," are *necessary* for rational behavior.

Evidence for such a hypothesis derives from experimental and clinical data, as well as from philosophical inquiry.

Comparative neurology (comparison of the brains of different animals) clearly supports the conclusion that there has been an enormous elaboration or differentiation of cortical areas involved both in emotion and in executive

function in the human brain. For example, the orbitofrontal cortex is one of the areas implicated in our ability to abstract—and to apply to our behavior—the "mores" of our cultures. Other parts of the prefrontal cortex, for example, the dorsolateral prefrontal cortex, are also highly differentiated in humans, and believed to play a critical role in executive functions.

Now, in addition to research data, the conclusion that emotions play a role in "rational" judgment has also been made by a number of contemporary philosophers.

Other experimental data derives from the field of moral psychology, wherein individuals are asked to choose, in a moral dilemma, between one option or another. Using fMRI, the brains of these individuals are studied to determine what areas are active during this moral decision process. The areas of the brain most activated under these conditions are the areas of the orbitofrontal cortex and other areas of the limbic system. When an individual makes morally neutral judgments, these areas of the brain are not activated.

The conclusion that emotions play a role in rational judgment has also been made by many contemporary philosophers. You are encouraged to peruse excellent discussions by a number of contemporary philosophers, including Robert C. Solomon and Ron DeSousa, as well as others listed in the bibliography at the end of the course. Very importantly, much of our understanding of the role of "feelings" in rational judgment, has come from the clinic. We will spend some time discussing the patient described briefly below.

The patient Elliot was initially described by Antonio Damasio in *Descartes' Error*. Elliot was a young man of high IQ who appeared to have undergone a major change in his personality after developing, and then having surgery to remove, a brain tumor; the damage to the brain involved both prefrontal cortices, with more damage to the right than the left; damage also occurred to the axons beneath the prefrontal area.

One of the most dramatic consequences of this damage was Elliot's loss of emotions—or more specifically—his loss of "feelings," or his own subjective sense of emotion. What was most enlightening about this case is that Elliot could no longer make rational decisions. He could discuss the pros and cons of various scenarios (e.g., his rational ability and IQ appeared to be intact), but he could no longer choose between them. Without emotions, he could not weigh the various options. This decision-making difficulty was most pronounced in the social and personal realms.

From this, as well as other observations, a new paradigm has emerged, one which acknowledges that our "feelings" play a major role in our ability to make "rational" judgments. This is believed to be of enormous adaptive advantage since it allows learning and memory—previous experience—and our "feelings" related to our experiences, to influence our present actions. Without emotions, we, like the patient Elliot, cannot act in our own best interest. ■

Suggested Reading

A. Damasio, *Descartes' Error.*

R. DeSousa, *The Rationality of Emotion.*

R. C. Solomon, *The Passions.*

R. C. Solomon, *True to Our Feelings.*

Questions to Consider

1. Do you ascribe personally to a variation of Dualism in your own thinking about emotion and rational thought? Why or why not?

2. In your own life how are you able to let emotions guide you to "good" decisions?

Processing of Negative Emotions—Fear

Lecture 28

We are going to look at one of the so-called emotions and its internal subjective experience. That emotion or internal subjective "feeling" that's generated is "fear." A great deal of research in neurobiology has gone towards understanding the brain mechanisms involved. I want to stress again that we may think of it as a negative emotion when we are afraid.

Strong emotions can be powerful to the point of paralyzing action. All animals, however, face threats to their survival, making it likely that brain mechanisms would have been selected for that allow a quick response to threat. Here we discuss the contribution of modern neuroscience in the discovery of the critical role played by a small almond-shaped subcortical nucleus called the amygdala in the rapid processing of sensory information signaling threat. This emotion is interpreted by the brain, and internally represented and experienced as fear. Activation of this nucleus is implicated in a number of disorders, including posttraumatic stress syndrome.

In the last lecture, we saw how emotions play an important role in our ability to make "rational" decisions. While it is not known how the subjective "feeling" or internal representation of fear is generated, we have learned a great deal about the nuclei which are involved in the processing of stimuli which signal or pose a threat to the organism.

The amygdala has emerged as a central player in the brain's circuits in which a stimulus is perceived as threatening, and an internal feeling of fear experienced by the individual. The amygdala is actually a large group of nuclei (the amygdaloid complex) that are part of the subcortical gray matter beneath the temporal pole. The function of the amygdala is to process sensory information in terms of emotional significance, and to coordinate the action of a variety of systems which allow for an appropriate response; the amygdala plays a critical role in "emotional" memory.

The amygdala has widespread, and generally reciprocal, connections to other brain areas including the neocortex, hippocampus, hypothalamus, and some nuclei of the extrapyramidal motor system. It receives a direct projection from sensory nuclei of the thalamus (bypassing the cortex); such a pathway allows for the rapid response to a potentially threatening situation.

Now, sadly, in our modern world, we often react to non-threatening stimuli as though they were threatening.

Much of our understanding of this rapid processing system has come from studies looking at *learned fear* in animals. In such studies, animals learn to fear something that is not intrinsically threatening. For example, rats learn to fear a grid on which they have previously received electrical shock. While we cannot know what the animal is "feeling" or experiencing, it will exhibit behaviors, including an increased vigilance, rise in blood pressure, and catecholamine and cortisol release, all of which are part of a stress response that prepares the animal for fight or flight.

- Four brain regions have been shown to play a critical role in learned fear, and in the "unlearning" of the fear response.

- Amygdala: Removal of the amygdala results in the loss of the learned fear response. Animals will no longer show a fearful response to threatening stimuli (either learned or intrinsically threatening).

- Hippocampus: This old cortical area is critical in learning and memory.

- Prefrontal cortex: This area appears to be critical for "unlearning" the behavior; even small lesions in animals can prevent unlearning of the response.

- Areas of the reticular formation: Areas of the reticular formation are known to play a role in "selective attention"; these areas are

also implicated in the shunting of sensory information directly from the thalamus to the amygdala.

PET scans and fMRI indicate that the same areas play a role in human disorders in which there is a heightened anxiety, panic, or fear. Individuals with *posttraumatic stress disorder* (PTSD), for example, show increased activation of the amygdala when experiencing attacks of panic and fear. Long-term sufferers of PTSD also show a decreased volume of the hippocampus, which is believed to be due to a prolonged stress response. As individuals with PTSD "recover," there is an increased activation of the prefrontal cortex, and a decreased activation of the amygdala.

OCD involves many of the same brain areas. OCD is characterized by chronic obsessive thoughts (for example, fear of germs) which lead to compulsive behaviors (like hand-washing). This disorder also underscores a relation between cognition, emotion, and behavior. Individuals with OCD show an increased activation of the amygdala, cingulate gyrus (a medially located limbic cortical area), and caudate nucleus (extrapyramidal motor system), and decreased activity of the prefrontal cortex. Both psychotherapy and treatment with SSRI antidepressants can be effective in the treatment of this disorder; fMRIs of patients benefiting from either treatment show a decreased activity of amygdala, cingulate gyrus, and caudate nucleus, and an increased activation of the prefrontal cortex.

In short-term threatening situations, it is obviously desirable to have a rapid and effective response. Sadly, in our modern world, we often react to nonthreatening stimuli like traffic jams as though our lives were being threatened. This produces a chronic stress response that has long-term deleterious effects on the body and brain. ■

Suggested Reading

J. LeDoux, *The Emotional Brain*.

Questions to Consider

1. Emotional memory is very recalcitrant to extinction. Think about your own lives. Are there past events, such as a car accident or other traumatic event, the emotional memory of which can be easily triggered? Why do you think the brain does not want to forget such events?

2. When something like abuse is very threatening, we may seem to forget. Given what you have learned in this class, would the brain *really* forget? Explain your answer.

Music and the Brain

Lecture 29

In this lecture I thought what I would do is use music as a theme to tie together information that we have covered about sensory systems and about emotional experience and also about language, even, because we are going to see that music involves all of these systems. We know that music is both a sensory and an emotional experience.

Our ability to write, read, and perform music requires the coordinated activity of all of these areas of the brain. Clinical studies of musicians who have suffered strokes suggest that specific brain areas are involved in various aspects of both the composition and appreciation of elements of music, such as rhythm. Finally, it is the involvement of limbic system structures that allows music to have such a powerful emotional impact on our lives.

Sensory systems: First and foremost music is an auditory experience. Music, as opposed to simple sound, however, is composed of *tones*; even a single tone is composed of many "sounds," including a fundamental frequency (the lowest and generally dominant sound in a tone), and "overtones." Music is heard and appreciated as a sequence of tones, not as individual sounds or frequencies (pitches); what is most important in musical perception is not even the individual tones, but the relationship between tones (this is why we can hear a melody in any key and recognize it).

Language: While there are many differences between music and language, there are also some striking similarities.

- Both show rhythm, tempo, and anticipation.
- In both, meaning is mapped to sound and/or to written symbols.
- Music can also be generated internally, much like internal thought.

- Similar to language, what music seems "natural" is the one you are exposed to as a child; thus, the Western diatonic scale seems like "real" music to the Western ear, but would not seem so to individuals from cultures with other musical traditions.

- Music, like language, shows *hemisphere dominance*; both right and left hemispheres appear to be equally good at processing pure frequency tones, but in nonmusicians, the right hemisphere is dominant for appreciation of melody and harmony, and the left hemisphere for rhythm.

- Music and language are both inventive, yet they follow rules.

- Music and language *communicate*!

Brain mechanisms: Music is an auditory experience involving auditory areas of the cortex. While primary auditory cortex (Area 41) may contribute to some "sharpening" of the fundamental frequency, tones in music are thought to be processed primarily by higher-order auditory association areas. *Amusia* (a form of music agnosia) can result from damage to auditory association areas; such individuals show a significantly diminished or loss of the ability to appreciate melodies, or some other aspect of music.

The limbic system is involved not just with the listener, but also with the person who's the performer or the composer.

Limbic system: For most individuals, music evokes pleasure, and thus must involve limbic system structures. Listening to music stimulates the endogenous reward system, and induces the release of endorphins; brain damage can result in a loss of the ability to experience emotion when listening to music. The hippocampus is also believed to be involved in the ability to remember long sequences of music. The cingulate gyrus, which is a limbic cortical area located medially above the corpus callosum, also appears to play a role in our appreciation of musical sequence, but it is not well understood.

Some of the most intriguing findings in this area of neuroscience have included a study of professional musicians, some of whom have sustained brain damage, for example, from stroke. In musicians, the left hemisphere is dominant for nearly all aspects of music; there is a shift in hemisphere dominance (compared to nonmusicians) from the right to the left hemisphere for the perception of melodies; the dominance of the left hemisphere in musicians may also contribute to their enhanced rhythm perception, as well as play a role in their superior musical memory.

At least in musicians, the loss of musical ability may occur from damage to "language" areas. For example, progressive left temporal lobe damage to Wernicke's area (Area 22) and adjacent parietal cortex (Areas 39, 40) in Maurice Ravel led to a Wernicke's aphasia, the inability to translate musical ideas into musical symbols (i.e., he could no longer write music), and eventually, amusia.

It is also well-known that each of us has a preference for a specific type of music, for example classical music or jazz. It is likely that preference for a type of music is related to a number of factors including musical history (what you have been exposed to especially as a child and adolescent), and temperament (the latter would also be involved in personality). There may be something in our individual neural wiring of auditory and limbic areas that makes some types of music "speak" to us while others do not. ■

Suggested Reading

R. Jourdain, *Music, the Brain, and Ecstasy*.

D. J. Levitin, *This Is Your Brain on Music*.

Questions to Consider

1. What kind of music do you most enjoy? Does it vary depending on your mood?

2. What emotion(s) do different types of music elicit in you?

Sexual Dimorphism of the Brain

Lecture 30

We have considered the human brain as though it were generic, focusing on a sort of general understanding of how different areas of the brain are involved in a variety of different functions. Here we are going to examine some of the data indicating that at least in some ways the brains of males and females are different.

Hormones exert a powerful influence on human behavior, as anyone who has experienced puberty can attest. It was the hormonal environment that existed in fetal life, however, that determined the "sex" of our brains long before puberty. At birth, our brains are sexually dimorphic, meaning that they are either male or female in pattern. Male and female brains can be distinguished on the basis of how particular structures are organized at gross, cellular, and even molecular levels. Moreover, since both male and female brains are compatible with either male or female body or phenotype, it is possible for a genetically and phenotypically normal male or female to have a brain of the opposite sex. Here we discuss both the neurobiology of sexual differences, which is relatively simple, and human sexuality, which is extremely complex. Lastly, while the most dramatic differences in gross brain structure appear to involve areas likely to be involved in sexual behavior and mating, how we experience and interpret the world may also be influenced by the sex of our brains.

"Sex" is a complicated subject; generally it is broken down into a number of different, but interrelated, categories.

- *Genotypic sex*, determined by the inheritance of either XX or XY chromosomes.

- *Phenotypic sex*, determined by the development of internal/external genitalia.

- *Gender identification* which, in humans, is determined by the subjective perception of one's sex; the latter is a construct created by the brain related to one's identity.

Neuroscience has revealed another category and that is *brain sex* meaning that there are actual structural (and thus likely functional) differences in the way the brain is organized in males and females. This is referred to as sexual dimorphism of the brain. An individual nucleus or structure is said to be sexually dimorphic if it differs in size, number or density of neurons, number or types of synaptic connections, or in the expression of particular receptors or other molecules in male and female brains.

[The scientist] doesn't say that the male brain or the female brain is better. It doesn't make evaluation. What it says is that the brains are different.

What induces sexual dimorphism of the brain? In developing males, immature testes produce testosterone, which is converted in the brain to estradiol; the presence of estradiol in the brain results in a "male" brain pattern. In developing female fetuses, the absence of significant levels of testosterone/estradiol causes the brain to develop as a "female" brain. The brain becomes sexually dimorphic during a critical period, or window of time, which in humans, occurs during fetal life; from that point, the brain sex is determined for life; thus at puberty, circulating testosterone and estrogen act on a brain that is *already* sexually dimorphic.

Most research in this area has been done on rats because the critical period for determining brain sex in rodents occurs after birth, allowing brain sex to be manipulated pre- and postnatally. For example, after birth during the critical period, female rat pups can be given testosterone, or males can be castrated. As adults, such animals will act and show behaviors related to their brain sex, and *not* to their genotype or phenotype.

What areas have been shown to be sexually dimorphic in humans? Many of the nuclei/areas believed to be sexually dimorphic are part of the limbic

system. Areas of the hypothalamus, especially those that play a role in mating and/or parenting behaviors. The hippocampus, which shows a significantly higher concentration of estrogen receptors in females; in adult females, circulating estrogens induce dendritic growth and increase spine density in the hippocampus. Differences in the amygdala, indicating that the sexes may differ in how they respond emotionally to stimuli.

There are other differences between male and female brains that may influence how information is processed. The male brain pattern results in an earlier and stricter hemisphere lateralization. This may underlie the finding that unilateral hemisphere damage in males generally results in more disability than in females; this is especially pronounced with respect to language dysfunction after left hemisphere damage. There is some evidence that the corpus callosum is either different in size or shape in males and females.

There are no overall differences between males and females in IQ and no significant differences between the sexes in the number of neurons. That does not mean, however, that males and females do not have different strengths. Females appear overall to show enhanced language ability and empathy, and ability to read emotion in other people; they also have a superior emotional memory. Males, on the other hand, are clearly superior in spatial ability and in their ability to build systems. In addition to any native differences that might exist, cultures around the world typically exaggerate the differences between males and females.

What, if any, is the evidence that sexual dimorphism of the brain influences behaviors such as choice of sexual partner? At least one of the sexually dimorphic nuclei identified in the hypothalamus is also dimorphic between hetero- and homosexual males, with the pattern in the homosexual brain being similar to the female pattern. The exact role this specific nucleus plays in sexual behavior in humans, however, is not known.

Some suggestion that choice of sexual partner in adults is related to brain sex comes from the study of a disorder known as adrenal hyperplasia. Individuals with this disorder are genotypically and phenotypically female; they have a male brain, however, because of an increased production of androgens

during the critical period of development. Individuals with this disorder are more likely to behave as tomboys as children, and they show an increased incidence of choosing females as sexual partners as adults. ■

Suggested Reading

S. Baron-Cohen, *The Essential Differences*.

D. Blum, *Sex on the Brain.*

L. Brizendine, *The Female Brain.*

S. LeVay, *The Sexual Brain.*

Questions to Consider

1. Summarize how the male and female brains are biologically different.

2. In what ways do you think male/female behaviors are *more* influenced by culture than by biology?

Sleep and Dreaming

Lecture 31

In the present lecture … we are going to touch just a little bit on what neuroscience is contributing to our understanding of an altered state of consciousness that we all experience every day, and that's sleeping and dreaming. It turned out that this was a lot more difficult than it first looked.

As infants, we spend a disproportionate amount of time sleeping. As adults, we worry about whether we are getting enough or too much sleep. But why do we sleep? And what, if anything, do dreams signify or mean? Do they provide us with divine inspiration or portent as the ancients believed, or do dreams give us a peek at unconscious processes as Freud suggested? Or are they simply the result of the random firing of neurons? In this lecture, we will attempt to address some of these questions by summarizing what has been discovered about how specific neural structures regulate sleeping and dreaming. Far from being a passive event, sleep is actively induced and involves areas of the CNS extending from the spinal cord to the forebrain. While we still cannot answer the question about the meaning of dreams, or even why we dream, we have learned a great deal about the different types of dreams which occur during various stages of sleep.

In previous lectures, we have been considering awake, cognitive behavior; we have avoided addressing what it means to "be awake," what it means to be conscious. In a following lecture, we will examine the current ideas and problems related to our understanding of the conscious state; here we will discuss what light modern neuroscience has shed on an altered state of consciousness that all of us experience: sleep and dreaming.

There are complex interactions between CNS nuclei that control wakefulness, and nuclei that control sleep and dreaming. Some of the areas involved include reticular formation. These are multiple nuclei distributed throughout the brainstem with widespread projections to the thalamus and/or cortex. The above neural groups are regulated by specific nuclei in the hypothalamus

which are critically involved in homeostatic mechanisms and light/dark cycle regulation of sleep and wakefulness; all of the circuits work together to control brain activity and to switch between states of wakefulness and sleep.

Changes in brain electrical activity, which can be measured by an *electroencephalogram* (EEG), are seen in various stages of sleep, which occur in 5–7 "cycles" per night. In slow-wave sleep, the EEG shows slow frequency, high voltage activity which is highly synchronized; heart rate, blood pressure, and respiration are decreased (e.g., there is parasympathetic dominance).

We spend about a third of our lives asleep. This in itself says that something important has to be going on. Yet we don't have any idea why we need to sleep or why we need to dream.

Rapid eye movement (REM) sleep is a *deeper* level of sleep; the first REM episode occurs within about 90 minutes of falling asleep. The EEG shows low voltage, fast, desynchronized activity, similar to the awake state (thus, REM sleep is also called "paradoxical" sleep), but the arousal threshold is significantly increased. The consumption of oxygen by the brain is greater during REM sleep than during either intense physical or mental exercise; heart rate, blood pressure, and respiration are increased and variable (e.g., there is sympathetic dominance). REM sleep in humans begins in utero; it decreases from infancy (around 50% of total sleep) till puberty (around 20%), then remains relatively stable.

There appear to be two general systems that regulate the states of sleeping and dreaming, both of which project directly to the cortex or project to the thalamus, which then projects to the cortex. One system involves nuclei that are primarily at the pons/midbrain junction. The other involves nuclei in the pons and the medulla and other areas that project to the cortex. During wakefulness, both of these systems are active. During slow wave sleep, there is a decrease in activity in both of the systems. During REM sleep, the first system is extremely active and the second system is completely turned off.

While we understand less about the mechanisms that control dreaming, we know that it is also regulated primarily by the reticular formation. All humans dream several times a night; dreaming occurs in both REM and non-REM sleep. There is an increased dream recall during REM sleep; REM "rebound" can occur if individuals are deprived of sleep. Over the course of a night, there is an increased intensity, with the emotional content of dreams and visual imagery greatest in the early morning.

"Bad" dreams, generally with complex imagery and stories, can occur during REM sleep. Dreams that occur during non-REM sleep are poorly recalled; dream content is more similar to waking cognition, and is generally less visual and less emotional.

True nightmares, however, are thought to occur only during non-REM sleep; such dreams are accompanied by respiratory oppression and difficulty breathing; there can be an almost complete skeletal muscle paralysis. In children, non-REM nightmares are called *pavor nocturnus* (or night terrors); these episodes can last 1–2 minutes; usually there will be no recall of the event. In adults, such nightmares are called "incubus" (for demon) and can be very intense; there is usually no memory of the dream; if there is any recall, there is no "story" to the nightmare; rather, the person reports single, horrifying events.

Sleep disorders include an inability to stay asleep, *somnolence* (sleepiness during the day), and narcolepsy (a genetic disorder manifested by episodes of suddenly becoming very sleepy or falling asleep during the day). When individuals with narcolepsy suddenly fall asleep, they go directly to REM. Individuals with this disorder also often have cataplexy, a sudden loss of muscle tone brought about by strong emotion.

Sleep research is an important—and very active—area; we spend ⅓ of our lives asleep, yet we do not know why we need to sleep or dream. But we do know that only animals with neocortex have REM sleep. REM is thought to be involved in helping in the consolidation of memory. Research in this area is also important for other reasons. For example, while dreams may appear real while sleeping, when we awaken, we can distinguish between dreams and reality; this ability to normally distinguish between dreaming and reality

is intriguing (and can be lost in some disorders); in the next lecture, we examine the enigma of the conscious state. ■

Suggested Reading

Any recent neuroscience text will cover most of the basic information covered in this lecture, although in much greater detail. The authoritative book in neuroscience is *Principles of Neural Science*, edited by E. R. Kandel, J. H. Schwartz, and T. M. Jessell.

Questions to Consider

1. Describe an instance when you dreamed the solution to a problem that faced you when awake.

2. Do you have recurring dreams? What do these dreams signify to you?

Consciousness and the Self

Lecture 32

We have been talking about topics like sleeping, and dreaming, and things like this … . These are very difficult subjects to investigate on an experimental level and certainly difficult to know what the experience is like for human beings. But of all the things that fascinate us as human beings, there is probably nothing that fascinates us more than the phenomenon of consciousness.

From whence comes the impression that a given experience is happening to a "me"? What is the "me"? What is consciousness? Are animals other than humans conscious? Do they have a sense of "self"? Do other animals possess a mind? Historically, such questions have not been considered amenable to scientific inquiry. The development of sophisticated tools for examining the function of the brain, as well as an accumulation of data on rare brain conditions, however, has reawakened an interest in these questions. While much remains to be elucidated, these approaches are revealing some of the neural mechanisms underlying consciousness, awareness, and sense of self-awareness.

Consciousness refers to an organism's awareness of itself and the world in a subjective sense; it involves awareness, attention, self-reference, and other qualities. Consciousness, as the term is used here, relates specifically to cortical processes that underlie our subjective experience, for example, of seeing, hearing, and being.

An analysis of consciousness presents a number of problems, which I think of as hard, harder, and hardest! The hard problem (referred to by some philosophers and neuroscientists as the "easy" problem of consciousness) involves the identification of the neural correlates of consciousness; it is termed "easy" because it is believed to be amenable to scientific investigation. Certainly some headway has been made in elucidating the neural connections and circuits that underlie the formation of specific percepts such as color vision. Other correlative data, generated from fMRI and other brain imaging methods, has shown what brain areas are active, for example, when an

individual is speaking or thinking or considering a moral dilemma. We also know that consciousness is maintained, at least in part, by projections from specific areas of the reticular formation to the thalamus and/or cortex; bilateral damage to these areas produces unconsciousness or coma. These nuclei and projections are part of the reticular formation referred to as the *ascending reticular activating system* (ARAS), and are necessary, but not sufficient, for the subjective aspects of consciousness.

The "harder" problem involves asking "Why?" "Why is neural activity accompanied by an internal subjective experience (*qualia*)?" "How and why does neural activity generate qualia?" These questions may not be answerable. Certainly not all neural activity is accompanied by a subjective experience; we are often on "auto-pilot," yet information is reaching our brains; even during anesthesia, information is reaching our cortex, but we do not act on it, nor remember it, because our ARAS is inhibited. Examples can also be given where animals are able to make complex visual discriminations, for example, in the (likely) absence of a "subjective" experience of vision. So, the question remains, "Why do we have subjective experience?" "Why, at least in humans, is the discrimination of wavelength accompanied by a subjective experience of color, for example?" "Could wavelength not be used for discrimination by an 'intelligent' zombie?"

Even if we identified every single area of the brain that contributed to a self, it still wouldn't answer the question about why we have a subjective experience of ourselves.

The "hardest" problem of consciousness involves examining why consciousness appears to be "something" that is happening to a "me," both in terms of subjective experiences *at this moment* and *over time*. In previous lectures, we have reviewed that our sense of "self" is an ever-evolving construction of the brain; many neural systems are involved, including the somatosensory system (feedback from the body), the hippocampus and other memory structures (that contribute to the creation of an "autobiography"), the posterior parietal cortex (which helps us distinguish self from nonself),

and probably many other areas as well. Again, however, identifying the underlying neural correlates does not answer the question as it is related to subjective experience.

To appreciate the difficulties in understanding what consciousness is, we need to return to a closer examination of some of the patients discussed in the lecture on agnosias. We will reexamine what is *actually lost* in cortical blindness, prosopagnosia, and contralateral neglect. For example, in cortical blindness (from damage to Area 17), the individual is actually not blind, but is unaware that they can see! Individuals with prosopagnosia cannot recognize a face among a group of faces—even that of their spouse; what they appear to have lost is not the recognition of "faces," but the ability to place an "identity" with a particular face. Like individuals with cortical blindness and prosopagnosia, those with contralateral neglect are not blind; they simply neglect or deny—or fail to have "awareness of"—the left half of the body and the world.

Throughout our course we have been talking about the multiple parallel pathways in the brain, yet everything that happens to "me" seems to be a unitary experience. Understanding how all of it comes together is referred to by neuroscientists as the *binding problem*.

If all of these questions are not difficult enough to ponder, imagine trying to view them from an evolutionary perspective: "Of what advantage is consciousness or self-consciousness?" "Why would a subjective experience of brain processing have been selected at all?" "Do other animals have self-awareness?" We are back to the problem of explaining, or at least hypothesizing about, the "why" of consciousness. ■

Suggested Reading

F. Crick, *The Astonishing Hypothesis.*

D. C. Dennett, *Consciousness Explained.*

C. Koch, *The Quest for Consciousness.*

R. Ornstein, *The Evolution of Consciousness.*

J. R. Searle, *The Mystery of Consciousness.*

Questions to Consider

1. There are notable individuals who do not believe there is any such thing as "consciousness." They believe that what we call consciousness is an illusion. What do you think?

2. If you believe consciousness exists, why do you think it has been selected for in evolution? What advantage might it confer upon those who possess it? What advantage would *self-awareness* confer?

Alzheimer's Disease

Lecture 33

It's clear from our previous lectures that the consequences of brain damage tell us a lot about the normal functioning of the brain. Sadly, this is especially true of Alzheimer's disease, a devastating disorder that has given us insight into the functioning of even the highest areas of the human brain.

Alzheimer's disease, first identified by Alois Alzheimer in 1907, is the number one neurological disease in the United States, affecting millions of people. Its impact as a disorder reaches far beyond the numbers of sufferers, or even the billions of dollars spent—to the emotional impact this disease inflicts on loved ones and caregivers. This devastating disease does, however, provide a glimpse into the role of some of the most higher-order areas of the human brain. While some of our current understanding will no doubt be modified by future findings, what is currently understood about this disorder gives us insight into what areas of the brain contribute to what defines us most as "human."

It should be clear from previous lectures that the consequences of brain damage tell us much about the normal functioning of different areas of the brain. Sadly, this has been especially true of Alzheimer's disease, a devastating disorder that has given us insight into the functioning of the highest areas of the human brain.

In 1907 Alois Alzheimer reported a case of a 51-year-old woman who had dementia (mental deterioration); at autopsy, her brain showed neuropathologic findings (e.g., neurofibrillary tangles and plaques) that are the hallmark of this disease. This disorder is sometimes classified into early (before age 65) and late (after age 65) onset forms; while there are genetic forms of the disease, they account for a very small fraction (about 5–10%) of cases. While a number of behavioral tests and scanning methods (for example, MRI and PET) can lend support for a positive diagnosis, Alzheimer's disease can be positively diagnosed only at autopsy.

There are a number of widespread changes in the CNS in this disorder. Neuron loss is most pronounced in the following areas:

- Neocortex, especially the higher-order association areas; primary areas remain relatively intact. Loss of neurons leads to cortical atrophy.

- Entorhinal cortex and hippocampus; both areas are known to play an important role in memory.

- Amygdala; affects the processing of information with an "emotional" content.

- *Nucleus basalis of Meynert*; a small nucleus of the reticular formation with widespread cholinergic projections to cortex without relaying through the thalamus; while the function of this tiny nucleus is unknown, its degeneration, under any conditions, is associated with dementia.

So for most of the cases [of Alzheimer's] there is no known cause, and for all cases there is no cure.

- Nucleus locus coeruleus; the tiny reticular formation nucleus in the pons utilizing norepinephrine as a neurotransmitter. This nucleus also has massive widespread projections to the neocortex with no relay in the thalamus. It plays a role in the regulation of blood flow, extraction of oxygen and glucose in the brain, selective attention, sleep/wake cycles, and other functions.

- Raphe nuclei; groups of neurons throughout the brainstem using serotonin as a neurotransmitter. They also have massive projections to the cortex without a relay in the thalamus.

Within neuron cell bodies abnormal twisted *filaments* (called neurofibrillary tangles) can be visualized. Neuritic "plaques," which are abnormal

depositions of a protein (beta amyloid) in the extracellular spaces of the brain. There is a massive loss of dendritic branches, spines, and synapses; it is estimated that hundreds of thousands of synapses a day can be lost with Alzheimer's disease! Abnormalities in blood vessels also result from this disease. The amyloid protein that is part of the plaques in this disease is also deposited in blood vessels throughout the body and brain; the breakdown of the vessel wall can result in cerebral hemorrhage.

Changes in the blood-brain barrier are also seen in Alzheimer's. Normally, there is a cellular barrier that prevents certain substances from entering the brain; when this breaks down, metals and other compounds flood into the brain causing damage; individuals with Alzheimer's disease show about 30 times the amount of aluminum, for example, in their brain tissue at autopsy.

The behavioral changes seen in the individual are primarily the result of damage to brain areas and structures previously discussed. Common early changes include the following:

- Slight memory loss; especially short-term memory.
- Decreased initiative; often reflected in a loss of interest in hobbies and personal hygiene.
- Depression.
- Faulty judgment.

As the disease progresses, the following changes take place:

- Significant memory loss.
- Subtle changes in "higher-order" functions such as the ability to understand jokes.

- Mood disturbances like agitation that may show diurnal variation; "sundowning," for example, is the presence of severe anxiety, fear, agitation, and hallucinations occurring generally in the evening.

Late in the disease the following symptoms are often manifested:

- Severe memory loss; including long-term memory.

- Loss of a sense of "self"; the individual no longer knows who they are; this is believed to be due, in part, to the degeneration of the left hippocampus which is essential for memories of facts and events; the brain uses declarative and episodic memory—in a creative process—to construct "autobiography"; one of the truly horrible things about this disease is that it robs the person of a sense of themselves, in part, because it robs them of the memories of their lives.

- Severe language difficulty; the individual becomes unable to speak or to understand language.

- Other psychiatric problems like paranoia and low impulse control.

At the present time, there is no known cause for most cases of Alzheimer's disease. For all cases, there is no cure. Drugs may help with the signs and symptoms, particularly early on in the disease. There are, however, a number of risk factors identified that increase or decrease the probability of getting this disease. These risk factors will be the focus of our next lecture. ■

Suggested Reading

J. Bayley, *Elegy for Iris.*

T. DeBaggio, *Losing My Mind.*

Questions to Consider

1. Think about the people and events that have made your life special. What would your life be without these memories?

2. If it was possible for Alzheimer's disease to be positively diagnosed, would you *want to know* if you had this dreaded disease? Why or why not?

Risk Factors for Alzheimer's Disease

Lecture 34

In this lecture we want to focus on what neuroscience is discovering about what factors increase, or what factors decrease, the risk of developing Alzheimer's. Now, even if you follow everything and you do everything the way you are supposed to, it doesn't mean that you might not get this disease; but there are risk factors which are associated, and so this is really important.

In the previous lecture, Alzheimer's disease was used as a clinical example to bring together much of the information learned in this course by showing that the signs and symptoms seen in patients can be understood by looking at the particular brain areas most affected in this disorder. In this lecture, we will discuss what has been learned about factors that either increase or decrease the risk of Alzheimer's disease. Much of our discussion will focus on the Nun Study, a study of Catholic Sisters showing a very low incidence of Alzheimer's disease. This and other studies indicate lifestyle and habits may contribute to the prevalence of this disorder, and suggest ways each of us can make positive lifestyle changes that may help ward off this dreaded disease.

While the cause is not known, there are a number of factors that either increase or decrease the risk of getting Alzheimer's disease. What we know about these risk factors has come from both basic and clinical research. Factors that increase risk include the following:

- Age!

- Inheritance of E4/E4 *alleles* (one from each parent) coding for *apolipoprotein E* (ApoE). Alleles are gene variants; there are three alleles in the normal population for ApoE; inheriting E4/E4 alleles is a major genetic risk/susceptibility factor in late onset familial (genetic) and sporadic (nongenetic) Alzheimer's disease. ApoE is normally involved in lipid (fat) metabolism and cholesterol transport in the body.

- Head injury at a concussion or more severe level.
- High fat diet, elevated cholesterol, and obesity.
- Atherosclerosis, diabetes, and hypertension.
- Smoking.
- A history of clinical depression.
- Diagnosis of mild cognitive impairment (MCI), which is characterized primarily by a short-term memory loss without other cognitive deficits; since the majority of individuals diagnosed with MCI go on to develop Alzheimer's disease, it may represent an early stage of the disease.
- Hormone replacement therapy; women taking estrogen alone or estrogen and progesterone may show an increased incidence of dementia if the regimen is begun at 65 years of age or older.

Factors that may decrease risk include the following:

- Inheritance of E2/E2 alleles for ApoE.
- Eating omega-3 fats (found in cold water fish like salmon).
- Maintaining a healthy weight, low fat diet, and low blood level of low-density lipoproteins.
- Drinking fruit and vegetable juice and teas rich in antioxidants.
- Exercise. Recent studies show that exercise actually promotes mitosis, or the generation of new neurons, in the hippocampus!
- Continuing mental activities that involve "learning" and "challenge."

Many of these risk factors were either discovered or confirmed in a large study of Catholic Sisters (called the Nun Study) which has been conducted for more than 20 years. It had been observed that in some convents, nuns were living into their hundreds, with little evidence of cognitive decline or dementia; these women were able to learn new foreign languages in their 90s! In an effort to help science understand their longevity and good mental health, they agreed to donate their brains to science upon death.

Life was meant to be lived every day. Live it with passion, live it with joy, and appreciate each moment of it and appreciate your brain and take care of it.

One of the most important findings from this study has been that the only nuns showing signs of Alzheimer's disease were those who also demonstrated evidence of micro infarctions (small strokes); there is now recognition that there is a comorbidity (occurrence together) of Alzheimer's disease and vascular disease (atherosclerosis). This association has been confirmed in experimental studies on animals (who do not get Alzheimer's disease normally); ischemia can induce neurofibrillary tangles and plaques in the brain. Note that the risk factors for Alzheimer's disease overlap with risk factors for development of heart disease.

Another interesting finding which emerged from the Nun Study was an analysis of writing samples indicating that those sisters who would later develop Alzheimer's disease showed a paucity of "ideas" and complexity in written language up to 50 years before diagnosis; sisters whose writing reflected a greater complexity of ideas and emotional content were significantly less likely to be later diagnosed with this devastating disease.

There is great variability in the reported changes that have been observed in the normal aging brain (for example, in neuron loss and/or atrophy); the Nun Study would suggest that contrary to widespread belief, significant cognitive decline is not, however, a normal part of aging.

In summary, the nuns who were studied had a lifestyle that contributed to being mentally healthy; they lived relatively low stress lives with others

with whom they shared similar viewpoints; they were well read, had good eating habits, and exercised regularly. So, to end this, I want to say, and in all seriousness, there are changes we can make in our life. Life was meant to be lived every day. Live it with passion, live it with joy, and appreciate each moment of it and appreciate your brain and take care of it. ■

Suggested Reading

D. Snowdon, *Aging with Grace.*

Questions to Consider

1. While we cannot control our genetics, many factors that increase the risk for Alzheimer's disease are under our control. How well do you follow the guidelines for a healthy heart and brain?

2. How do you challenge your brain?

Wellness and the Brain—Effects of Stress

Lecture 35

We are going to look at what happens when you have a chronic activation of the system. It's hoped that this is just going to reinforce what you already know is true, and that is it's important to decrease stress in your life, but now you will have some real evidence as to why you want to be able to do this.

The Nun Study and many others, in addition to common sense, suggest that decreasing stress is likely to contribute to the quality of life. Why? Early in our history, our survival depended on recognizing and responding to potentially life-threatening situations, and our brain has mechanisms which evolved to allow for an acute, rapid response to such events by preparing us for fight or flight. Unfortunately, in our modern world, we respond to everyday stressors as though they are life-threatening events. In this lecture, we will review evidence that chronic activation of this system has deleterious effects on both the immune and cardiovascular systems, and more recent studies indicating that it may also cause direct damage to the brain.

It has become increasingly clear that how we interpret and experience the world emotionally has a profound effect on our physical and mental health. Interpreting and responding appropriately to a potentially threatening stimulus is important for survival; in a previous lecture, we learned that the amygdala is part of a brain circuit that allows a rapid response to potentially threatening stimuli; under such circumstances, our nervous system prepares us for fight or flight.

Stress stimulates the activation of part of the nervous system under the control of the hypothalamus (sympathetic nervous system) which causes the release of *adrenocorticotropic hormone* (ACTH) from the pituitary. Release of ACTH in turn causes the release of catecholamines (especially of epinephrine) and the stress hormone cortisol from the *adrenals* (glands located above the kidneys) into the bloodstream. These processes are useful and nondamaging in the short-term; they result in an increased alertness,

stimulation of muscle, and other physiological changes that allow us to meet a challenge; when the crisis is over, another part of the nervous system (the parasympathetic nervous system), also under the control of the hypothalamus, returns the system to balance or homeostasis.

Chronic or frequent stress, however, induces changes which are damaging to both the immune and the cardiovascular systems. Within the immune system, chronically high cortisol levels are associated with a decrease in the body's natural immune response, a decrease in DNA repair mechanisms, and an increase in *autoimmune* mechanisms.

The better coping skills we develop, then the kinder we are to our bodies and our brains.

Within the cardiovascular system, cardiovascular disease is linked both to dietary habits, and to chronic stress. In chronic stress, the heart muscle can be damaged directly (referred to as nonischemic cardiac damage) by high levels of catecholamine release; similar damage can be produced in animals by injecting epinephrine into the bloodstream. Chronic stress also exacerbates coronary heart disease, which can lead to ischemic damage of the heart; this is brought about by damage to the walls of arteries, which promotes the build-up of cholesterol, and to an increase in platelet clumping; these changes occur in the arteries of both the heart and the brain, thus increasing the risk of stroke as well.

There is accumulating evidence that chronic stress can lead to neuron death in the brain. The most compelling evidence comes from studies showing that chronic stress causes neuron loss in the hippocampus (referred to as hippocampal atrophy); neurons in the hippocampus have a high concentration of receptors that bind cortisol, and long-term elevated cortisol levels induce changes that result in the death of these neurons. Increased hippocampal *atrophy* can be seen in adults who were abused as children, individuals who suffer from long-term depressive illness or prolonged grief, as well as in individuals with PTSD.

What has emerged from clinical psychology/counseling, psychiatry, and neuroscience, is that the response to stress is dependent on the individuals'

"perception" of the event. Except in extreme cases, it is not the stressor itself that is important, but our perception of it. The susceptibility of structures like the hippocampus to chronic stress would indicate that to increase the quality of our lives requires us to respond appropriately to stressors and to learn coping skills that help maintain homeostasis. ■

Suggested Reading

B. McEwen, *The End of Stress as We Know It.*

R. M. Sapolsky, *Why Zebras Don't Get Ulcers.*

Questions to Consider

1. It has been said that we cannot change the wind, but we can control the set of our sails. Do you believe that you are at the mercy of your emotions, or that you have the ability to control your reactions to events? Explain your answer using examples from your own life.

2. How does your "personality" change when you are under prolonged stress? Is your reaction to stress wreaking havoc in your personal life?

Neuroscience—Looking Back and Looking Ahead

Lecture 36

Here we have tried to stay with sort of a global appreciation of the brain so that you can understand how it's organized, how it functions, or at least how we think it functions, and also basically to just help you learn about what kinds of questions neuroscientists are interested in asking. And maybe a little bit of the insight into why some of the questions are very, very difficult.

We have just scratched the surface of what is known in neuroscience—and what is known is only a small part of what is yet to be known. Moreover, information is rapidly changing even our most basic conceptions of how the brain works. It is hoped that this course has informed and amazed, as well as generated interest in this dynamic field of science.

This lecture will summarize the main overall conclusions that can be drawn from what we have learned about the brain, and about the relationship between mind and brain. We will also discuss some of the challenges facing neuroscience, as well as how on some fronts, we are making headway in understanding some major neurologic/psychiatric disorders. We will conclude with a more theoretical discussion of why it would be limiting, however, for us to view the human mind only in terms of biology.

What are the main conclusions that might be drawn from the information covered in this course? The brain, and not the heart or the ventricles, gives rise to the mind! Everything we see, hear, feel, and think, and all that we can do, is the result of underlying brain processes; the corollary to this is that anything can be taken away with the correct brain lesion. Our emotions can be a positive force in our lives, guiding us in making rational decisions; we can learn to modify our reactions to events, and to use our emotions to help guide us in decision making that enhances the quality of our lives. Our brains are "plastic"; this ability makes it possible for us to continually learn from our experiences in ways that can enrich our lives. We should treat our

brains with respect. We cannot control our genetics, but we can control many factors that contribute to a healthy, active brain.

What are some of the challenges facing modern neuroscience? Unraveling the cause and mechanisms of many neurologic/psychiatric disorders. Some important advances have been made in our understanding of many disorders such as Alzheimer's disease, multiple sclerosis, autism, attention-deficit disorder, and schizophrenia—but much more remains to be learned.

We've made the best inroads in disorders that have a genetic component, but we also need to learn more about the forms of these and other sporadic disorders that do not appear to have a genetic component. We also need to spend a great deal of effort determining how we can help individuals who already have these disorders.

Understanding individual differences; ultimately, we would like to understand, for example, why some individuals are scarred for life from abuse, and others, whose abuse appears objectively greater, are not. We have much to learn about the gene-environment interface in the development of each of us as a unique human being.

- Understanding more global or distributed brain processes that underlie not only consciousness, but also intelligence and creativity.

- Understanding the brain processes underlying human behavior in the social realm. We are social beings, and our brains are shaped, not just by experience in the world of objects, but by interactions with other humans. This area is just beginning to receive attention in modern neuroscience.

For example, there is evidence that humans may have an instinct for morality, similar to an instinct for language. Areas of the brain have been identified that play a role in our ability to feel empathy. Moreover, we have evidence from the clinic that individuals who commit multiple murders or who have certain types of sociopathy do not show activation of these "empathy" neurons when they view the suffering of other people.

Lastly, we need to think beyond neuroscience to what it means to *be human*. This question cannot be answered by science. Certainly, our ability to reason, to feel, to abstract, or even to be moral—are the result of underlying neural mechanisms. Learning about these mechanisms in the brain will give us some insight that will be helpful in living enriched lives with others. Our final conclusion in the course might be that life—and in humans the awareness of it—is an incredible gift. What a journey we're on, and it is all due to this amazing brain! ■

Suggested Reading

M. D. Hauser, *Moral Minds.*

Questions to Consider

1. What is the most amazing thing you learned about the brain from this course?

2. What other major conclusions have you drawn about how the brain works from this course?

Glossary

Note: In the following glossary, a definition of the term as it is used throughout this course is given rather than a comprehensive definition.

action potential: A change in membrane potential arising at the axon hillock; it travels down the axon in an all-or-none fashion.

adrenal glands: Glands located above the kidneys; under stress, they release catecholamines and cortisol.

adrenocorticotropic hormone (ACTH): A hormone released from the anterior part of the pituitary of the hypothalamus.

agnosia: "Without knowledge"; an inability to recognize some aspect of an object, for example, what it is, on the basis of sensory input.

allele: A gene variant inherited from each parent.

Alzheimer's disease: A degenerative neurological disorder characterized primarily by the loss of neurons in higher-order regions of the neocortex, limbic system structures, and specific reticular formation nuclei with widespread projections to the cortex.

amacrine neurons: Interneurons in the retina.

amotivational syndrome: A behavioral complex characterized by inattention, lethargy, and apathy; often associated with long-term use of marijuana.

amusia: A form of music "agnosia" occurring from lesions to higher-order auditory areas in the temporal lobe.

amygdala: An almond-shaped nucleus beneath the rostral pole of the temporal lobe; involved in the processing of emotions, particularly fear.

amyotrophic lateral sclerosis (ALS): Also called Lou Gehrig's disease or motor neuron disease, this neurological disorder is characterized by the loss of motor neurons throughout the central nervous system.

anterior horn cells: Large motor neurons located in the anterior horn (gray matter) of the spinal cord.

aphasia: An acquired disorder of language.

apolipoprotein E: A protein normally involved in cholesterol transport; inheritance of the E2 or E4 alleles is associated with lower or higher plasma cholesterol and decreased or increased risk for Alzheimer's disease, respectively.

area: Generally a nucleus, or collection of neurons, involved in a particular function.

ascending reticular activating system (ARAS): Nuclear groups that are part of the reticular formation; these nuclei stimulate the thalamus and cortex to allow for consciousness to occur.

association cortex: "Higher-order" neocortex involved in multimodal or cognitive functions.

association pathways: Bundles of axons connecting neurons of different lobes within one hemisphere.

astrocyte: Star-shaped glial cells derived from the same progenitor cells that give rise to neurons.

atrophy: Shrinkage or degeneration of neurons or an area.

autoimmune: An immune response directed against one's own tissue.

axon: The process of a neuron specialized for the transmission of information; axons are the physical structures that connect different areas of the brain.

axon collateral: A branch of a main axon arising from a node or break in the myelin sheath.

axon hillock: The area of the neuron where the axon begins and where the action potential is generated.

basal ganglia: A number of nuclei located subcortically in the forebrain. Many of the basal ganglia nuclei are involved in the extrapyramidal motor system.

bilateral: Pertaining to both sides.

binding problem: How perception and experience appear (subjectively) to be "unitary," while arising from multiple separate pathways and areas.

biogenic amine theory of depression: The theory that depression results from a functional deficiency of monoamines within particular pathways/ structures of the central nervous system.

biogenic amines: In the context of how the term is used in this course, it refers to the monoamine neurotransmitters dopamine, norepinephrine, and serotonin.

bipolar disorder (manic depression): An illness characterized by wide mood swings ranging from severe depression to expansive mania.

bipolar neurons: Interneurons intercalated between photoreceptors and retinal ganglion cells.

brain sex: A male or female pattern of brain development occurring as the result of hormonal influences during a critical period; referred to as "sexual dimorphism" of the brain.

brainstem: A phylogenetically older area of the brain consisting of the midbrain, metencephalon, and myelencephalon.

Broca's aphasia: A motor or "expressive" aphasia caused by damage to Areas 44 and 45 of the frontal lobe in the left (dominant) hemisphere.

Brodmann's areas: Numbered cortical areas first delineated by Korbinian Brodmann on the basis of cytoarchitecture.

cataract: A clouding or opacity of the lens due to biochemical changes in the lens structure itself.

catecholamines: The neurotransmitters dopamine, norepinephrine, and epinephrine.

caudal: Toward the back.

central canal: The remnant of the opening of the neural tube in the spinal cord of the adult.

central nervous system (CNS): The part of the nervous system comprising the brain and spinal cord.

central sulcus (of Rolando): A major sulcus (or fissure) on the lateral aspect of the hemispheres, separating the frontal and parietal lobes.

cephalic: Toward the head.

cerebellum: Part of the metencephalon; involved in motor coordination and some cognitive functions.

cerebral cortex: The outer sheet or mantle of cells covering the hemispheres.

cerebrospinal fluid (CSF): A fluid made within some of the ventricles of the brain.

cerebrum: Generally, this term is used in reference to the structures of the telencephalon.

cingulate gyrus: A ring of cortical tissue above the corpus callosum; gives rise to a major association pathway called the cingulum.

cingulum (girdle): Association fiber bundle consisting of axons of cingulate gyrus neurons which connect various lobes within each hemisphere.

circle of Willis: An arterial "circle" at the base of the brain formed by the union of the carotid and basilar/vertebral arteries.

cochlea: Fluid-filled structure of the inner ear.

cognitive/cognition: Related to mental activities such as thinking, learning, and memory.

color agnosia: One type is the loss of the ability to see "color," even though the ability to distinguish different wavelengths of light is intact.

commissural pathways: Axons of neurons connecting areas of the two hemispheres.

commissure: Bundles of axons crossing the midline of the brain to connect areas in both hemispheres.

comparative neurology: The study of the brain across different animal species.

computed tomography (CT): Basically x-rays that have been enhanced by computer algorhythms to reveal fine structure.

concussion: A transient disruption of brain function; may, but does not always, involve an alternation of consciousness.

cones: Six million photoreceptors specialized for vision under high light conditions; responsible for high visual acuity (form vision) and color vision; most numerous in the macula and fovea of the retina.

consciousness: The awareness of oneself and the world in a subjective sense.

construct: As used here, underlying cognitive processes that allow for ideas to be formed that guide behavior in some way.

contralateral: Opposite; often used in reference to lesions.

contralateral neglect: A condition resulting from damage to the right posterior parietal cortex where (generally) the left side of the body and world are "ignored" or neglected.

cornea: Transparent outer layer of cells of the eyeball through which light must pass.

corpus callosum: The largest axon commissure in humans, connecting homotopic parts of the cortex in each hemisphere.

cortex: The outer "bark" or mantle of the two cerebral hemispheres.

cortical blindness: A condition in which an individual with damage to cortical areas reports that they are "blind."

cranium: The skull.

critical period: A window of time in which some process must take place.

cytoarchitecture: The way in which neurons are arranged into groups or layers.

decussate: To cross the midline of the brain.

dementia: A progressive mental deterioration.

dendrites: "Trees"; true extensions of the neuronal cell body, increasing the surface area of neurons.

depolarization: A cellular process in neurons in which there is a change in the membrane potential; results when the inside of the neuron becomes more positive; increases the probability that an action potential will be generated at the axon hillock.

depression: A disorder of "mood" characterized by an internal subjective state of hopelessness and despair.

diencephalon: A subdivision of the adult central nervous system derived from the prosencephalon in development; consists of two major areas, the thalamus and hypothalamus.

differentiation: Specialization of a tissue or an area of the brain.

discriminative touch (fine touch): The system that allows for the recognition of the size, shape, and texture of objects; comparable to the "cone" system of the retina.

dopamine: One of the catecholamine neurotransmitters/neuromodulators in the CNS; the major neurotransmitter used by ventral tegmental neurons.

dorsal: Referring to the upper surface.

dorsolateral prefrontal cortex: Involved primarily in executive functions; contributing to our ability to prioritize behavior and adapt to change.

Dualism: The belief that mind and body are distinct entities, independent and different in nature.

dysphoria (crash): An extremely unpleasant subjective state characterized by depression, irritability, and anxiety.

ear drum (tympanic membrane): The membrane that "vibrates" when sound waves enter the external ear canal.

edema: "Swelling" generally caused by a collection of fluid from a variety of sources.

electroencephalography (EEG): Gross recording of the electrical activity of the cortex.

emotion: A basic, physiological state characterized by identifiable autonomic or bodily changes.

endogenous: "Within."

endogenous reward system: A subsystem of the limbic system, activation of which produces feelings of well-being.

entorhinal cortex (Area 28): A neocortical area involved in learning and memory.

epistemology: A branch of philosophy involved in the study of knowledge.

extrapyramidal motor system: A large number of complexly interconnected nuclei that play a role primarily in motor programs and in some types of motor learning. The nuclei of the extrapyramidal motor system do not project to the spinal cord; they indirectly influence the direct and indirect corticospinal pathways.

extrastriate visual areas: Any of the "higher-order" visual areas of the cortex lying outside of Area 17.

feeling: The internal, subjective state associated with an emotion.

fissure: A deep folding of the cortex.

foramen magnum: The hole in the skull where the brain (specifically the medulla) is continuous with the spinal cord.

forebrain: The rostral part of the brain that represents the most recently evolved areas phylogenetically.

fovea/fovea centralis: The center of the macula and area of the retina specialized for the highest visual acuity.

frontal lobe: The lobe of the cortex bordered posteriorly by the central sulcus of Rolando and inferiorly by the Sylvian (lateral) fissure.

gamma-aminobutyric acid (GABA): A major inhibitory neurotransmitter of the CNS, particularly of interneurons.

ganglion (pl. ganglia): A group of cell bodies in the peripheral nervous system; comparable to a nucleus in the central nervous system. Some structures in the central nervous system (e.g., basal ganglia) are also referred to as ganglia.

gender identification: The subjective perception of one's sex.

genotypic sex: Sex determined at conception (XX or XY).

gestation: Pregnancy.

glaucoma: A disorder due to increased intraocular pressure; can damage the retina and/or optic nerve to cause irreversible blindness.

glia: Supporting cells of the brain, some of which are derived from the same precursor cells as neurons; other glia are derived from other embryonic tissue.

glutamate: An amino acid neurotransmitter; the major excitatory neurotransmitter in many of the pathways of the central nervous system.

gray matter: Areas where there are collections of neuronal cell bodies.

gyrus: The crests or elevations of cortical tissue.

hard-wiring: Genetically determined developmental orchestration of long-axon pathways connecting nuclei within different systems.

hemisphere: The two large structures of the telencephalon, consisting of cortex, underlying axons, and deep nuclear structures (like the basal ganglia).

hemisphere dominance: The idea that a particular function is primarily regulated by only one of the two hemispheres.

hemorrhage: A bleed.

herniation: Movement of a structure; in neurology, this generally refers to the movement of the brain as the result of space-occupying lesions.

hindbrain: The posterior part of the brainstem, includes the metencephalon and myelencephalon.

hippocampus: A phylogenetically old cortical area of the temporal lobe involved in learning and memory.

homeostasis: "Balance"; as used here, for example, balance between sympathetic and parasympathetic portions of the autonomic nervous system.

homotopic: "Same."

homunculus: Distorted figure of a "man" mapped onto brain regions in motor and somatosensory areas.

horizontal organization of the cortex: Division of the cortex into Brodmann's areas.

hyperpolarization: A cellular process in neurons in which there is a change in the membrane potential; occurs when the inside of the neuron becomes more negative, thus decreasing the probability of the generation of an action potential at the axon hillock.

hypothalamus: Diencephalic area involved in homeostasis; provides the autonomic outflow to the body for the limbic system.

idiopathic: Generally in medicine, this means "cause unknown."

indirect corticospinal pathways: Pathways involved in a variety of functions, including maintenance of background "tone" in muscle.

indolamine: A molecule with a particular structure; here, it refers to the monoamine serotonin (5-HT).

infarct/infarction: An area of cell death resulting from the loss of blood supply.

intention tremor: A tremor or involuntary movement which is primarily seen at the end of a movement, particularly when a fine motor movement is made.

interneuron: Small neurons with short axons that do not project outside of a nucleus; they are integrative in function, intercalated between input and output of a structure.

ion: A charged atom.

ion channel: Generally a protein that regulates the flow of ions, for example, across a membrane.

ipsilateral: A reference term meaning same side; often used in reference to brain lesions or damage.

ischemia: A loss of blood supply to an area, due to physical obstruction, for example, by plaque.

ischemic penumbra (umbrella): Area surrounding an ischemic stroke where neurons are at risk because of glutamate toxicity.

lateral: Away from the body midline.

lateral geniculate nucleus (LGN): A multi-layered nucleus in the thalamus which receives information from parts of both eyes; neurons of the LGN project to the primary visual cortex (Area 17).

learned fear: A "fear" response which is acquired to a stimulus that is not intrinsically threatening.

lens: Transparent flexible structure that allows for objects at different distances to be brought into focus.

lesion: Damage.

leukotomy: Undercutting of the axons going to and from an area.

limbic system: A collective term for a large number of interconnected nuclei and areas of the brain involved in learning, memory, emotion, and executive function.

lobes: Subdivisions of the cortex.

lobotomy: Removal of a cortical lobe.

long-axon neurons: Neurons whose axons make up the associational, commissural, and projection pathways.

macula/macula lutea: The central area of the retina where light rays are focused; contains a yellow pigment to absorb short-wavelength light.

magnetic resonance imaging (MRI)/functional magnetic resonance imaging (fMRI): A computer-assisted imaging that uses powerful magnets to create detailed images of soft tissue; functional MRI refers to the additional method of visualizing what areas of the brain are active or functional by their utilization of oxygen.

manic depression: See bipolar disorder.

medial: Toward the body midline.

medial geniculate nucleus (MGN): The major nucleus in the thalamus involved in audition; neurons of the MGN project to the primary auditory cortex (Area 41).

medulla/medulla oblongata: The myelencephalon; continuous with the spinal cord at the foramen magnum.

mesencephalon: Midbrain; the area of the brain lying between the diencephalon and the pons of the metencephalon; also used to denote the embryonic tissue from which the adult midbrain is derived.

metencephalon: The pons and cerebellum of the adult brain.

midbrain: The adult subdivision of the brain lying between the diencephalon and the pons of the metencephalon; derived from the mesencephalon in development.

midline: Midline of the body.

migration: As used here, the movement of neurons or cells away from a mitotic zone.

mild cognitive impairment (MCI): Characterized primarily by a short-term memory loss without other cognitive deficits.

mind: The seat of consciousness and cognition; the subjective experience of underlying neural processes.

mitotic: Referring to a cell's ability to undergo division or mitosis.

monoamines: As used here, refers to the catecholamines (dopamine and norepinephrine), and serotonin (5-HT).

mood: An emotional response that fluctuates.

morpheme: The simplest arrangement of phonemes into meaningful groups (for example, a syllable).

motion agnosia: An agnosia where an individual loses the subjective sense of "motion."

multimodal: Involving more than one sensory system.

multiple sclerosis: An autoimmune disorder of the central nervous system in which auto-antibodies are made against oligodendrocytes and myelin.

multipolar: Used to refer to neurons that have many processes emanating from the cell body.

myelencephalon: The medulla or medulla oblongata.

myelin sheath: A fatty sheath around axons that increases the speed of conduction; the sheath is a lipid (fat) wrapping around axons formed by oligodendrocytes.

natural ligand: A naturally occurring molecule in the body/brain that binds to an endogenous receptor.

nerve: A pathway or tract.

neural plate: Undifferentiated neural cells.

neural tube: Tubular structure formed by the proliferation of neural plate cells.

neurofilament: Tiny filamentous thread-like structures that are part of the cytoskeleton of axons.

neuromodulators: Molecules similar to neurotransmitters that are released from the presynaptic terminal and diffuse across the synaptic cleft to bind to molecules or receptors in the postsynaptic membrane.

neuron: Specialized cells of the nervous system.

Neuron Doctrine: The principle that neurons are the structural and functional units of the nervous system.

neuropore: In development, the top and bottom openings of the neural tube.

neurotransmitter: Molecules released from the presynaptic terminal that diffuse across the synaptic cleft to bind to molecules or receptors in the postsynaptic membrane.

neurotubule: Tubelike structures within axons involved in the transport of substances from the cell body to the axon terminal; also part of the cytoskeleton of the axon.

nociceptive: Literally, "to injure"; the senses of pain and temperature.

node: Breaks in the myelin sheath along myelinated axons.

norepinephrine: The major neurotransmitter of the nucleus locus coeruleus ("blue" nucleus), a tiny nucleus in the pontine reticular formation involved in sleep/wake cycles, attention, and regulation of blood flow.

nucleus: In neuroscience, a collection of neuron cell bodies into a structure with unique cytoarchitecture, connections, and function.

nucleus accumbens septi: A forebrain nucleus which receives its major input from the ventral tegmental area; plays a role in reward and in addiction.

nucleus basalis of Meynert: A tiny nucleus of the rostral-most part of the reticular formation; has widespread projections, some of which do not relay through the thalamus, to the cerebral cortex; utilizes acetylcholine as a neurotransmitter.

nucleus locus coeruleus (blue nucleus): Small nucleus in the pontine reticular formation; utilizes norepinephrine as a neurotransmitter.

obsessive-compulsive disorder (OCD): A disorder characterized by chronic obsessive thoughts and behaviors.

occipital lobe: A cortical lobe located at the posterior pole of the brain and demarcated by a line from the parieto-occipital sulcus to a notch in the temporal lobe.

oligodendrocyte: A glial cell of the central nervous system derived from the same progenitor cells as neurons; their main function is to myelinate axons in the central nervous system.

ontology: A branch of philosophy dealing with the meaning of existence.

opioids: Naturally occurring "morphine-like" peptides in the brain.

optic disc: The area of the retina where the axons of retinal ganglion cells leave the eye (blind spot).

optic nerve: A nerve bundle or pathway consisting of the axons of retinal ganglion cells.

orbitofrontal cortex: A part of the frontal lobe involved in impulse control, inculcation of cultural mores, and ability to appreciate the consequences of one's behavior.

organ of Corti: The part of the cochlea containing the receptor neurons (hair cells) for the auditory system.

organelle: Internal cell structures; for example, mitochondria are organelles within cells of the body, including the neurons of the central nervous system.

oxytocin: The "love" molecule; a peptide hormone released by the hypothalamus; plays a role in a number of processes, including "bonding" in social animals.

parasympathetic nervous system: Part of the peripheral autonomic nervous system associated with "rest and digest" functions.

parietal lobe: A cortical lobe bordered by the central sulcus of Rolando anteriorly, the parieto-occipital sulcus posteriorly, and the Sylvian (lateral) fissure inferiorly.

Parkinson's disease: A neurodegenerative disease resulting from the loss of neurons in the substantia nigra of the midbrain; characterized by a resting tremor, abnormal posture, and paucity of normal movement.

pathway: A collection of axons; also called tracts or nerves.

percept: The mental image formed from the stimulation of sensory systems; mental "ideas."

perception: The mental process or act of awareness of an object or idea.

peripheral nervous system (PNS): The parts of the nervous system (neurons, pathways) that lie outside of the brain and spinal cord.

phenotypic sex: Sex determined by development of internal/external genitalia.

phonemes: The individual distinct sounds of a language.

phrenology: A discipline whose main tenets included that mental faculties are located in specific cortical areas and that the development of such faculties could be judged by the size of the overlying skull areas.

phylogenetic: Evolutionary.

pitch: Roughly, the perception of frequency, although the correspondence between pitch and frequency is not exact.

polarized: Directional; in terms of neuronal structure, this refers to the fact that part of the neuron is specialized for reception of information from other neurons (e.g., the dendrites and cell body), and another part of the neuron (e.g., the axon) is specialized for transmitting information to other neurons.

pons: A part of the metencephalon; called "the bridge" because it connects the brain with the cerebellum.

positron emission tomography (PET): An imaging method utilizing radioactive tagged glucose or oxygen to examine the metabolism and activity of neurons.

postsynaptic: Describing the structure of the synapse having receptors which interact with neurotransmitters/neuromodulators to produce changes in synaptic potential; generally a dendrite or spine.

posttraumatic stress disorder (PTSD): A disorder characterized by anxiety and fear acquired because of a traumatic event.

prefrontal cortex: Part of the frontal lobe implicated in working memory.

presbycusis: Decreased hearing at higher frequencies which occurs from the loss of the flexibility of the basilar membrane with aging.

presbyopia: A disorder of vision occurring as the result of the loss of flexibility of the lens.

presynaptic: Describing the structure of the synapse containing neurotransmitter vesicles; generally an axon.

processes: Extensions emanating from the cell body of neurons or glial cells; the processes of neurons are the dendrites and axon.

projection pathways: Axons arising from neurons in one nucleus projecting to another area or nucleus.

propagate: To conduct or to move along (an axon).

proprioception: An awareness of where our limbs are; can be static (limbs at rest) or dynamic (limbs moving).

prosencephalon: The embryonic vesicle at the rostral end of the neural tube that differentiates into the telencephalon and diencephalon of the adult brain.

prosody: The musical nature of a language.

prosopagnosia: The inability to attach an identity to a particular face.

pupil: Variable aperture through which light passes into the eye.

pyramidal motor system: The part of the motor system involved primarily in the initiation of a motor movement.

quadriplegia: Paralysis of all four limbs; can occur following damage to the spinal cord at cervical (neck) levels.

qualia: The subjective "quality" of an experience, for example, the experience of "blue."

raphe nuclei: Small groups of serotonergic neurons of the reticular formation extending from the medulla to the midbrain.

rapid eye movement (REM): A state of sleep, also called "paradoxical sleep"; EEG during REM is similar to the "awake" state, although rapid eye movement is a deeper level of sleep. Dream content during rapid eye movement sleep is often recalled and includes complex stories and imagery.

rational: Related to reasoning.

receptor: A protein that binds to other molecules, for example, a neurotransmitter; also the name given to various types of sensory neurons that respond to particular modalities, for example, rods and cones are visual sensory receptor neurons.

resting membrane potential: The electrical potential across a membrane when the neuron is not being stimulated (about -70 mV).

resting tremor: A shaking, generally of the distal extremity like the hand, present when the individual is at rest, or not making a movement.

reticular formation: A collection of neuronal groups (greater than 100) in the core of the brain, running from the upper spinal cord/medulla into the telencephalon, that control a number of vital functions.

retina (neural retina): Multilayered sheet of neurons located at the back of the eyeball, and derived from the diencephalon in development.

retinal ganglion cells (RGCs): The neurons whose axons leave the eye to project to a variety of structures in the brain, including the lateral geniculate nucleus of the thalamus.

retinotopic: An ordered representation of the retina onto brain structures; while most are point-to-point, the maps may be distorted with areas of greatest importance (for example, the fovea in humans) having the greatest representation.

rhomboid fossa: The opening in the neural tube over which the cerebellum will develop.

rods: The 120 million photoreceptors specialized for vision under low light conditions; most numerous in the periphery of the retina.

rostral: Toward the head end.

sagittal: Midline.

saltatory conduction: "Jumping" conduction, meaning that the change in electrical potential jumps from node to node along myelinated axons.

sensation: The result of stimulation of sense organs; can also be a "feeling" in the somatosensory system.

serotonin (5-HT): Neurotransmitter/neuromodulator utilized primarily by raphe (midline) nuclei of the reticular formation which extend from the medulla to the midbrain.

short-axon neurons: Small neurons whose axons synapse within the nucleus where their cell body is located.

signs/symptoms: In neurology, signs are what is found on examination of the patient, while the symptoms are what the patient complains of; for example, increased reflexes found on neurological examination are signs, while a headache would be a symptom.

soft-wiring: Changes, particularly in synaptic connections, which occur as the result of experience.

somatosensory system: A sensory system conveying information the brain uses to construct percepts that we experience as pain, temperature, touch, and proprioception.

somatotopic: An orderly representation of the body in central structures; areas of the body with the most sensitivity (for example, the tips of the fingers in humans) may have a greater amount of central nervous system tissue devoted to them.

somnolence: Sleepiness.

space-occupying lesion: Any structure/damage that takes up space in the brain, for example, a tumor or a blood clot.

spines: Tiny protrusions of dendrites that greatly increase the surface area of the receiving part of neurons; generally postsynaptic.

stroke: Any acute neurological event related to impairment in blood flow or circulation in the central nervous system; can be hemorrhagic or ischemic.

subcortical: Beneath the cortex.

substantia nigra (black substance): A nucleus in the midbrain consisting of melanin-containing neurons; the nucleus, which is part of the extrapyramidal motor system, specifically degenerates in Parkinson's disease.

sulcus/sulci: The infoldings or valleys between the gyri of the cortex.

Sylvian (lateral) fissure: A major fissure or infolding of cortical tissue on the lateral surface of the hemispheres.

sympathetic nervous system: The part of the peripheral autonomic nervous system involved with the "fight or flight" response.

symptoms: *See* **signs/symptoms**.

synapse: The specialized junction between neurons, generally between the axon of one neuron and the dendrites/spines of another neuron. A synapse is composed of a presynaptic component with synaptic vesicles, a synaptic cleft, and a post-synaptic component.

synaptic cleft: The physical separation between pre- and postsynaptic processes at a synapse.

synaptic plasticity: The dynamic property of synapses; believed to underlie learning and memory.

synaptic potential: A change in membrane potential that occurs postsynaptically; can be excitatory or inhibitory; for excitatory synaptic potentials, the size of the synaptic potential is related to the amount of neurotransmitter released.

synaptic vesicles: Membrane-bound structures in presynaptic processes containing neurotransmitters.

telencephalon: In the adult brain, the two hemispheres.

temperament: Stable, in part genetically determined, personality characteristics related to the individual's way of engaging emotionally.

temporal lobe: A cortical lobe bordered dorsally by the Sylvian (lateral) fissure and the parieto-occipital/temporal notch posteriorly.

thalamus: A major structure of the diencephalon; composed of a number of individual nuclei, many of which project to the cortex, giving it the name "anteroom."

tone: A complex sound consisting of a fundamental frequency and series of overtones related to the fundamental frequency.

tonotopic: An orderly representation in central nervous system structures of the pitches resulting from the vibration of the basilar membrane; while generally point-to-point, "sounds" of greatest significance (for example, in humans, sounds associated with language) have the greatest representation.

tract: A pathway or nerve.

transient ischemic attack (TIA): An ischemic stroke which is transitory.

transporter: Proteins that span a membrane and can thus interact with extracellular molecules like neurotransmitters and affect their movement across membranes.

unilateral: One-sided.

ventral: Referring to the under surface of the brain.

ventral tegmental area (VTA): A small group of dopaminergic neurons in the midbrain involved in "endogenous" reward; considered part of the limbic system.

ventricle: Literally holes in the brain that develop from the central area of the neural tube; cerebrospinal fluid is made within some of the ventricles in the adult brain; once thought to be where the soul or mind resided.

vertical organization: Columns extending through the cortical layers that form a functional "module."

visual field: What the individual "sees."

visual object agnosia: A condition where the individual can "see" an object, but fails to recognize "what it is" using vision.

Wernicke's aphasia: A sensory or "receptive" aphasia; occurs from damage to part of Area 22 of the temporal lobe in the left (dominant) hemisphere.

white matter: Axons; in the fresh brain, the myelin sheath surrounding axons gives it a "whitish" appearance.

Biographical Notes

Many of the individuals highlighted below had complex views on the nature of humankind as well as the role of reason and emotion in human existence; therefore, brief sketches cannot possibly do justice to their ideas. For the sake of brevity, the following contains only a very brief description of a few of the historically important individuals who are specifically mentioned in the outlines. I have focused primarily on early natural philosophers/scientists, physicians, and anatomists whose work or ideas were pivotal in the development of modern neuroscience. Most philosophers, especially those around the time of the Enlightenment and after, were particularly interested in questions about how we know about the world, what constitutes the "categories" of our minds, and other questions of relevance to neuroscience. For the influence of modern philosophical thought, primarily related to either questions of the role of emotions in human behavior or the *meaning* of consciousness, I would direct the reader to books in the bibliography in Part III by Robert Solomon, David Chalmers, and John Searle, among others.

I would also direct the interested student to the website: www.nobelprizes.com/. Nearly one-third of all of the Nobel Prizes in Medicine or Physiology from 1901 to the present have been awarded to individuals whose work relates to neuroscience. A number of Nobel laureates, including Francis Crick, Gerald Edelman, and Eric Kandel have written books in neuroscience that are listed in the bibliography.

Alois Alzheimer (1864–1915). Pioneering German physician and neuropathologist who in 1901 first described a 51-year-old patient (Auguste D.) with advanced dementia, including severe memory loss and aphasia. When the patient died in 1906, Alzheimer described the cortical tangles and plaques that are associated with this disorder, thus helping to establish evidence of an organic cause for "presenile dementia" (now called early onset dementia). Alzheimer had worked at one time with Franz Nissl, and by using Nissl stains, he also documented the neuronal atrophy that characterizes this disorder. In addition, Alzheimer reported that Auguste D. showed evidence of atherosclerosis and blood vessel abnormalities, which

may have resulted in her death. Modern neuroscientists and pathologists now know that changes in blood vessels, and thus blood flow to the brain, are likely to precede the actual neuropathologic changes in the brain that are associated with Alzheimer's disease.

Aristotle (384–322 B.C.). Greek philosopher, student of Plato, and tutor to Alexander the Great; considered the founder of Western scientific thought. He held that "goodness" was defined by the realization of whatever function something was designed for; in humans, this meant the use of reason. He believed the brain's function was to cool the passions of the heart.

Paul Broca (1824–80). French physician and anthropologist who in 1861 published a seminal paper describing a patient who could understand spoken language but who could not speak language fluently; this language disorder was later referred to as Broca's aphasia. On autopsy, the site of the brain damage was identified by Broca as the left inferior frontal gyrus (Brodmann's Areas 44 and 45). This discovery helped establish that higher-order cognitive functions like language could be lost with specific brain lesions.

Korbinian Brodmann (1868–1918). German physician who worked with or was influenced by a number of prominent neurologists/psychiatrists, including Alois Alzheimer. Brodmann applied the recently developed "Nissl" stain to a comparative study of the mammalian cortex. The cytoarchitectural maps of the cortex in a variety of species, including human, supported the conclusion that the cortex of all mammals was organized similarly. The human cortex was subdivided into around 50 areas. While more modern methods have resulted in a greater subdivision of the primate cortex based on subtle anatomical and biochemical characteristics, Brodmann's numbering system is still widely used today.

Leonardo da Vinci (1452–1519). Italian artist, scientist, and quintessential Renaissance genius; his drawings of the ventricular cavities in the brain were more anatomically correct than any done before. Leonardo believed that the ventricles were the site of both cognition and perception, assigning specific functions, like imagination, to individual ventricles. We now know that the ventricles are the structures responsible for the manufacture and circulation of cerebrospinal fluid (CSF) in the brain.

René Descartes (1596–1650). French philosopher and mathematician; his philosophy championed Dualism, maintaining that there existed an immaterial rational soul separate and distinct from the material body. He postulated that the pineal glands represented the structure in the body where this immaterial soul or mind might interact with and influence the body (in spite of the fact that it was widely known that animals, which according to Descartes would not possess a rational soul, had large pineal glands!). According to some historians of neuroscience, however, it was Galen who first suggested that the pineal gland might play a role in the regulation of "spirits" in the brain. It is now known that the pineal is a gland that produces a number of substances involved in circadian rhythms.

Claudius Galen (c. 130–200 A.D.). Greek physician, philosopher, and scientist who ministered to both Roman emperors and gladiators during his career; he rejected the previously held belief that the heart was the seat of the soul or mind. He did, however, believe that vital spirits arose from the heart, and that these spirits were made "noble" in the brain. His lecture *On the Brain* was delivered to medical students in 177 A.D. Galen was the authority on medicine until the 16th century.

Franz Joseph Gall (1758–1828). German anatomist who championed that mental functions (around 30 separate organs or faculties) could be localized to the brain, specifically to the outer cortex of the hemispheres, and that development of these functions resulted in changes in the overlying bone of the skull. His work became the basis for the field of phrenology. While justly criticized for the lack of scientific evidence for these theories and for their later use to justify racism, it should be appreciated that his idea that it was the brain and not the heart that was the seat of the mind was truly revolutionary.

Camillo Golgi (1843–1926). Italian anatomist who developed the Golgi impregnation method where silver is deposited inside of neuronal cell bodies and dendrites, but not axons, in the adult CNS. Because only a fraction of the neurons within an area will impregnate, it has been used to examine the dendritic arbors of individual identified neurons. Golgi believed that the brain consisted of one large neural "net" or reticulum and not individual nerve cells. Santiago Ramón y Cajal, using Golgi's method, which in young

animals impregnates axons, was able to follow axons in the developing brain and establish that neurons are individual cellular units. Golgi and Cajal shared the Nobel Prize in 1906.

Franz Nissl (1860–1919). German physician and neuroanatomist who "accidentally" discovered that particular dyes (now called "Nissl" stains) were especially effective in staining neurons. It is now known that these dyes stain intracellular structures that are abundant in neuronal cell bodies and proximal dendrites. Nissl stains are still used to identify nuclei and cell groups in the nervous system.

James Papez (1883–1958). Comparative neuroanatomist who gave his name to one of the most important feedback circuits of the limbic system. The Papez Circuit was important in establishing the existence of specific neural pathways in the forebrain integrating memory and emotion.

Johannes Purkinje (1787–1869). Czech physiologist and anatomist for whom the Purkinje cells of the cerebellum are named. As a physiologist, he is best remembered for his contribution to our understanding of color vision, showing that our perception of color changes depending on background illumination.

Santiago Ramón y Cajal (1852–1934). Spanish anatomist considered by most neuroscientists as the greatest neuroanatomist who has ever lived. He used the Golgi method in young animals to establish that neurons were the fundamental cellular units of the nervous system, thus establishing the Neuron Doctrine that has guided neuroscience to this day. Cajal shared the 1906 Nobel Prize with Camillo Golgi.

Luigi Rolando (1773–1831). Influential Italian anatomist who helped champion the idea that brain functions could be localized to specific areas of the cortex. His work focused primarily on the pre- and postcentral gyri that constitute the motor and somatosensory areas, respectively. The sulcus that separates these two gyri and the frontal lobe from the parietal lobe is named for Rolando.

Charles Sherrington (1857–1952). English physiologist who named the "theoretical" junction between nerve cells in gray matter the "synapse." He shared the 1932 Nobel Prize with another great physiologist, Edgar Adrian.

Franciscus Sylvius (also called Franz de le Boë or François du Bois; 1614–72). German-born Dutch physician, chemist, and anatomist. A number of structures in the brain were named by Sylvius, including the Sylvian Fissure on the lateral surface of the brain separating the temporal lobe from the frontal and parietal lobes, and the Aqueduct of Sylvius, which is part of the ventricular system of the brain.

Karl Weigert (1845–1904). German neuropathologist who developed a stain for the myelin sheath surrounding neurons. The Weigert stain is commonly used for both normal and pathologic material. Generally, this stain is used in conjunction with a cell stain of contrasting color so that both nuclei and pathways can be visualized.

Karl Wernicke (1848–1905). German physician who in 1874 published a paper describing a patient with a language disorder later referred to as Wernicke's aphasia. The patient could speak, but not understand, language. Damage was found primarily (but not exclusively) to the superior temporal gyrus (Brodmann's Area 22). Along with Broca, Wernicke established that language was a left hemisphere function and that components of language (for example, speaking or understanding) can be dissociated with particular brain lesions.

Thomas Willis (1621–75). English physician and anatomist who was among the first to describe many neurological and psychiatric syndromes and to attribute them to disorders of the brain. Willis is considered the father of neurology. Willis published *The Anatomy of the Brain and Nerves* in 1664, a work that was complemented by the drawings of Christopher Wren, later England's great architect.

Christopher Wren (1632–1723). Great English astronomer, mathematician, and architect, best known for the design of St. Paul's Cathedral in London. Earlier, he had worked with Thomas Willis, providing the drawings for Willis's *Anatomy of the Brain and Nerves* (1664).

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———. and M. M. Scariano. *Emergence*: *Labeled Autistic.* New York: Warner Books, 1996. T. Grandin writes about her early experiences—and how she has come to view herself as a "recovering" autistic individual. Very interesting.

Haddon, M. *The Curious Incident of the Dog in the Night-Time*. New York: Vintage Books, 2003. A novel written from the perspective of an autistic individual.

Hauser, M. D. *Moral Minds.* New York: Harper-Collins, 2006. Excellent discussion of morality in all of its dimensions; argues that humans have an instinct for morality.

Jamison, K. R. *Exuberance*. New York: Alfred Knopf, 2004. Outstanding discussion of the role of "joy" in life and the possible neurobiological correlation. Highly recommended.

———. *An Unquiet Mind*. New York: Vintage Books,1995. Excellent first-person account by a psychiatrist with bipolar disorder.

Jourdain, R. *Music, the Brain, and Ecstasy*. New York: William Morrow, 1997. Excellent book on music and the brain—and what neural structures underlie our ability to appreciate melody and other characteristic features of music.

Kandel, E. R. *In Search of Memory*. New York: W. W. Norton, 2006. Outstanding book by a Nobel Prize winner—and very personal, yet also very informative, discussion of his life and career as a neuroscientist. Highly recommended.

———, J. H. Schwartz, and T. M. Jessell, eds. *Principles of Neural Science.* New York: McGraw-Hill, 2000. This is the authoritative text in neuroscience; may be difficult reading for the beginner.

Kegan, R. *The Evolving Self*. Cambridge, MA: Harvard University Press, 1982. A wonderful nonneuroscience book on the development—and personal and social evolution—of the *self*. Highly recommended.

———. *In Over our Heads: The Mental Demands of Modern Life*. Cambridge, MA: Harvard University Press, 1999. Wonderful nonneuroscience discussion of our continuing development as adults.

Kimmel, M. S. *The Gendered Society*. New York: Oxford University Press, 2000. Excellent book written by a male feminist about how society creates—or accentuates—differences between males and females.

Klawans, H. L. *Toscanini's Fumble and Other Tales of Clinical Neurology*. New York: Bantam, 1988. Excellent and interesting case studies in neurology.

———. *Newton's Madness.* New York: Harper Books, 1991. More unusual and interesting cases from clinical neurology.

———. *Trials of an Expert Witness*. New York: Little, Brown and Co., 1991. Discussion of famous legal cases where Klawans acted as a medical expert in clinical neurology.

Knapp, C. *Drinking: A Love Story.* New York: Dell Books, 1996. Book by a talented writer who suffered from both alcoholism and anorexia. Excellent for understanding the power of addiction.

Koch, C. *The Quest for Consciousness.* Englewood, CO: Roberts and Company Publishers, 2004. Outstanding discussion of consciousness in all of its complexity. Highly recommended.

Konner, M. *The Tangled Wing*. New York: Henry Holt, 2002. Updated classic book on the evolution of emotions.

Kramer, P. D. *Against Depression*. New York: Penguin Press, 2005. Follow-up book looking at depression historically as a "disease"; raises some important points about how depression is viewed by society.

———. *Listening to Prozac*. New York: Viking Press, 1993. Highly recommended for anyone interested in depression; raises a number of important ethical issues about the use of psychoactive drugs.

LeDoux, J. *The Emotional Brain.* New York: Simon and Schuster, 1996. One of the classics on emotions and brain structure.

———. *Synaptic Self.* New York: Penguin Books, 2002. Excellent book on how nature and nurture influence synaptic networks to *create* who we are.

LeVay, S. *The Sexual Brain*. Cambridge, MA: MIT Press, 1993. Excellent book by the neurobiologist who was among the first to discover differences between the brains of homosexual and heterosexual men.

Levitin, D. J. *This is Your Brain on Music.* New York: Dutton Press, 2006. Wonderful book on the human love affair with music written from multiple perspectives including neuroscience.

Margalit, A. *The Ethics of Memory*. Cambridge, MA: Harvard University Press, 2002. A little difficult to read at times, but worth it. Discussion of the importance of remembering horrific events like the Holocaust highlights that for humans, there is an "ethics" of memory.

McEwen, B. *The End of Stress as We Know it*. Washington, DC: Joseph Henry Press, 2002. Discussion of the evolution of a system in the brain to

deal with stress, and the toll of our modern world in terms of stress and the brain. Excellent.

Nagel, T. "What Is It Like to Be a Bat?" In *The Mind's I,* D. Hofstadter and D. Dennett, eds. New York: Basic Books, pp. 391–414, 1981. This reprinted article is a classic and highly recommended.

Norden, M. *Beyond Prozac*. New York: Regan Books, 1995. Discussion of the relationship between toxic lifestyles and relationships to depression.

Ornish, D. *Love and Survival*. New York: Harper Collins, 1998. Discussion of the powerful role of love and intimacy to good health.

Ornstein, R. *The Evolution of Consciousness*. New York: Simon and Schuster, 1991. Discussion on how consciousness may have evolved—and why.

Penrose, R. *The Large, the Small and the Human Mind*. Cambridge, UK: Cambridge University Press, 1997. A physicist looks at questions related to "mind" and "brain."

Pert, C. *Molecules of Emotion*. New York: Scribner, 1997. Excellent popular book detailing one woman's struggle in becoming a scientist—and how along this journey she made pivotal discoveries about opiate peptides; includes discussion of how the brain and immune systems may be interconnected. Excellent.

Pinker, S. *The Blank Slate*. New York: Viking Press, 2002. Revisit by an eminent cognitive neuroscientist of the nature/nurture debate.

———. *How the Mind Works*. New York: Norton Books, 1997. An excellent—but lengthy book—on the relationship between mind and brain.

———. *The Language Instinct*. New York: Harper, 1995. Very good book about the evolution of language.

———. *Words and Rules*. New York: Basic Books, 1999. An interesting—but very detailed discussion—of language/linguistics.

Quartz, S. R. and T. J. Sejnowski. *Liars, Lovers, and Heroes: What the New Brain Science Reveals about How We Become Who We Are*. New York: William Morrow, 2002. Explores how culture and development interact to form our "identities."

Ramachandran, V. S. *A Brief Tour of Human Consciousness*. New York: PI Press, 2004. Delightful and insightful discussion of interesting neurological cases and what they tell us about consciousness.

Ratey, J. J. and C. Johnson. *Shadow Syndromes*. New York: Pantheon, 1997. Discussion of "unconscious" psychiatric disorders and how they can influence behavior.

Restak, R. *The Brain Has a Mind of Its Own.* New York: Harmony Books, 1991. Anecdotal accounts of a practicing neurologist; interesting reading. Any books by this prolific writer are recommended.

Ridley, M. *The Origins of Virtue*. New York: Penguin Books, 1996. Excellent book on how virtue may have evolved in humans; stimulating reading—makes you think!

Rosenfield, I. *The Strange, Familiar, and Forgotten.* New York: Vintage Press, 1993. Outstanding and original analysis of neurological cases and their relevance for understanding consciousness.

Sacks, O. *An Anthropologist on Mars*. New York: Alfred Knopf, 1995. More interesting cases from neurology, including the discussion of the autistic woman Temple Grandin.

———. *The Man Who Mistook His Wife for a Hat*. New York: Touchstone, 1998. Interesting cases from clinical neurology.

Sapolsky, R. M. *Why Zebras Don't Get Ulcers.* New York: W. H. Freeman, 1998. Enjoyable and very readable book about the effects of stress on the brain.

Schacter, D. L., ed. *Memory Distortion.* Cambridge, MA: Harvard University Press, 1995. Extremely interesting book of articles exploring how individuals and societies distort reality—and why.

Searle, J. R. *The Mystery of Consciousness.* New York: New York Review of Books, 1997. Very readable and thought-provoking discussion of more philosophical aspects of what it means to be "conscious."

Snowdon, D. *Aging with Grace*. New York: Bantam Books, 2001. Wonderful book summarizing the Nun Study—to determine what life factors allow these women to live long, productive lives—without dementia.

Solomon, R. C. *The Passions.* Indianapolis: Hackett Publishing, 1993. Reviews the history of the myth that emotions and rational thought are at odds with each other.

———, ed. *Thinking about Feeling.* New York: Oxford University Press, 2004. Readings by contemporary philosophers on emotion. Excellent.

———. *True to Our Feelings.* New York: Oxford University Press, 2007. Wonderful book about how our emotions help give meaning to our lives. Highly recommended.

———. *What Is an Emotion?* New York: Oxford University Press, 2003. Excellent selection of pivotal writings on emotion from antiquity to the modern era on emotions.

Stewart, M. *The Courtier and the Heretic*. New York: W. W. Norton, 2006. Excellent read about two very influential thinkers (Leibniz and Spinoza) that have shaped our modern views.

Styron, W. *Darkness Visible.* New York: Vintage Books, 1990. Discussion by an eminent author of his own struggle with depression. Highly recommended.

Tannen, D. *You Just Don't Understand*. New York: Ballantine Books, 1990. Excellent book on how men and women communicate differently; important for all of us, but particularly for anyone interested in language and gender.

Tattersall, I. *Becoming Human.* New York: Harcourt Brace, 1998. Excellent book by an evolutionary biologist and prolific writer. It tries to tackle the question of the cognitive "gap" between humans and other primates.

Vertosick, F. *When the Air Hits Your Brain*. New York: Fawcett Crest, 1996. Interesting neurosurgical cases.

Vygotsky, L. *Thought and Language*. Cambridge, MA: MIT Press, 1992. A little dated, but an excellent discourse on the influence of language on thought processes.

Wiesel, E. *Memoirs: All Rivers Run to the Sea*. New York: Alfred Knopf, 1995. Outstanding autobiography by a man who was in a concentration camp as a teenager. Relates to the importance and ethics of memory in human life.

Wills, C. *The Runaway Brain*, New York: Basic Books, 1993. Good book on the evolution of the brain.

Wright, R. *The Moral Animal*. New York: Vintage Books, 1994. Evolutionary biologist's examination of how morality may have arisen. An intellectually stimulating book.

Zimmer, C. *Soul Made Flesh.* New York: Free Press, 2004. Excellent reading on the discovery of the brain as the seat of the mind, and possibly the soul. Highly recommended for anyone interested in the history of neuroscience.

Internet Resources

National Institutes of Health Institutes, Centers, and Offices. This website has links to numerous government-sponsored sites that provide information related to neuroscience, such as the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Mental Health (NIMH), the National Institute on Drug Abuse (NIDA), the National Institute on Aging (NIA), and the National Eye Institute (NEI). www.nih.gov/icd.

The Nobel Prize Internet Archive. "Nobel Prize in Physiology or Medicine Winners 2006–1901." Nearly one-third of all of the Nobel Prizes in Medicine or Physiology from 1901 to the present have been awarded to individuals whose work relates to neuroscience. A number of Nobel laureates, including Francis Crick, Gerald Edelman, and Eric Kandel, have written books in neuroscience that are listed in this bibliography. www.nobelprizes.com.